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Donepezil for dementia due to Alzheimer's disease (Review)

Birks JS, Harvey RJ

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[Intervention Review]

Donepezil for dementia due to Alzheimer's disease

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ABSTRACT

Background

Alzheimer's disease is the most common cause of dementia in older people. One approach to symptomatic treatment of Alzheimer's disease is to enhance cholinergic neurotransmission in the brain by blocking the action of the enzyme responsible for the breakdown of the neurotransmitter acetylcholine. This can be done by a group of drugs known as cholinesterase inhibitors. Donepezil is a cholinesterase inhibitor.

This review is an updated version of a review first published in 1998.

Objectives

To assess the clinical efficacy and safety of donepezil in people with mild, moderate or severe dementia due to Alzheimer's disease; to compare the efficacy and safety of different doses of donepezil; and to assess the effect of donepezil on healthcare resource use and costs.

Search methods

We searched Cochrane Dementia and Cognitive Improvement's Specialized Register, MEDLINE, Embase, PsycINFO and a number of other sources on 20 May 2017 to ensure that the search was as comprehensive and up-to-date as possible. In addition, we contacted members of the Donepezil Study Group and Eisai Inc.

Selection criteria

We included all double-blind, randomised controlled trials in which treatment with donepezil was administered to people with mild, moderate or severe dementia due to Alzheimer's disease for 12 weeks or more and its effects compared with those of placebo in a parallel group of patients, or where two different doses of donepezil were compared.

Data collection and analysis

One reviewer (JSB) extracted data on cognitive function, activities of daily living, behavioural symptoms, global clinical state, quality of life, adverse events, deaths and healthcare resource costs. Where appropriate and possible, we estimated pooled treatment effects. We used GRADE methods to assess the quality of the evidence for each outcome.

Main results

Thirty studies involving 8257 participants met the inclusion criteria of the review, of which 28 studies reported results in sufficient detail for the meta-analyses. Most studies were of six months' duration or less. Only one small trial lasted 52 weeks. The studies tested mainly donepezil capsules at a dose of 5 mg/day or 10 mg/day. Two studies tested a slow-release oral formulation that delivered 23 mg/day. Participants in 21 studies had mild to moderate disease, in five studies moderate to severe, and in four severe disease. Seventeen studies were industry funded or sponsored, four studies were funded independently of industry and for nine studies there was no information on source of funding.

Our main analysis compared the safety and efficacy of donepezil 10 mg/day with placebo at 24 to 26 weeks of treatment. Thirteen studies contributed data from 3396 participants to this analysis. Eleven of these studies were multicentre studies. Seven studies recruited patients with mild to moderate Alzheimer's disease, two with moderate to severe, and four with severe Alzheimer's disease, with a mean age of about 75 years. Almost all evidence was of moderate quality, downgraded due to study limitations.

After 26 weeks of treatment, donepezil compared with placebo was associated with better outcomes for cognitive function measured with the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog, range 0 to 70) (mean difference (MD) -2.67, 95% confidence interval (CI) -3.31 to -2.02, 1130 participants, 5 studies), the Mini-Mental State Examination (MMSE) score (MD 1.05, 95% CI 0.73 to 1.37, 1757 participants, 7 studies) and the Severe Impairment Battery (SIB, range 0 to 100) (MD 5.92, 95% CI 4.53 to 7.31, 1348 participants, 5 studies). Donepezil was also associated with better function measured with the Alzheimer's Disease Cooperative Study activities of daily living score for severe Alzheimer's disease (ADCS-ADL-sev) (MD 1.03, 95% CI 0.21 to 1.85, 733 participants, 3 studies). A higher proportion of participants treated with donepezil experienced improvement on the clinician-rated global impression of change scale (odds ratio (OR) 1.92, 95% CI 1.54 to 2.39, 1674 participants, 6 studies). There was no difference between donepezil and placebo for behavioural symptoms measured by the Neuropsychiatric Inventory (NPI) (MD -1.62, 95% CI -3.43 to 0.19, 1035 participants, 4 studies) or by the Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) scale (MD 0.4, 95% CI -1.28 to 2.08, 194 participants, 1 study). There was also no difference between donepezil and placebo for Quality of Life (QoL) (MD -2.79, 95% CI -8.15 to 2.56, 815 participants, 2 studies).

Participants receiving donepezil were more likely to withdraw from the studies before the end of treatment (24% versus 20%, OR 1.25, 95% CI 1.05 to 1.50, 2846 participants, 12 studies) or to experience an adverse event during the studies (72% vs 65%, OR 1.59, 95% 1.31 to 1.95, 2500 participants, 10 studies).

There was no evidence of a difference between donepezil and placebo for patient total healthcare resource utilisation.

Three studies compared donepezil 10 mg/day to donepezil 5 mg/day over 26 weeks. The 5 mg dose was associated with slightly worse cognitive function on the ADAS-Cog, but not on the MMSE or SIB, with slightly better QoL and with fewer adverse events and withdrawals from treatment. Two studies compared donepezil 10 mg/day to donepezil 23 mg/day. There were no differences on efficacy outcomes, but fewer participants on 10 mg/day experienced adverse events or withdrew from treatment.

Authors' conclusions

There is moderate-quality evidence that people with mild, moderate or severe dementia due to Alzheimer's disease treated for periods of 12 or 24 weeks with donepezil experience small benefits in cognitive function, activities of daily living and clinician-rated global clinical state. There is some evidence that use of donepezil is neither more nor less expensive compared with placebo when assessing total healthcare resource costs. Benefits on 23 mg/day were no greater than on 10 mg/day, and benefits on the 10 mg/day dose were marginally larger than on the 5 mg/day dose, but the rates of withdrawal and of adverse events before end of treatment were higher the higher the dose.

PLAIN LANGUAGE SUMMARY

Donepezil for people with dementia due to Alzheimer's disease

Review question

What effects (benefits or harms) does donepezil have on people with dementia due to Alzheimer's disease?

Background

Alzheimer's disease is the most common cause of dementia. As the disease progresses, people lose the ability to remember, communicate, think clearly and perform the activities of daily living. Their behaviour may also change. In severe Alzheimer's disease people lose the ability to care for themselves.

The most commonly used treatment for Alzheimer's disease are medicines known as acetylcholinesterase inhibitors. Donepezil is one of these medicines. It is taken as a pill once a day.

In Alzheimer's disease, one of the changes in the brain is a reduced number of nerve cells called cholinergic neurones. These are nerve cells that signal to other cells using a chemical called acetylcholine. Acetylcholinesterase inhibitors, such as donepezil, work by preventing acetylcholine from being broken down. This may improve the symptoms of dementia. However, acetylcholine is also found elsewhere in the body and so drugs of this type may have unwanted effects.

Review methods

In this review we examined evidence about benefits and harms from studies that compared donepezil, taken for at least 12 weeks, to placebo (a dummy pill), or that compared different doses of donepezil. The studies had to be double-blind and randomised, that is, the decision whether people taking part got donepezil or placebo had to be made randomly and neither they nor the researchers should have known which treatment they were getting while the trial was going on. This was to make the comparison as unbiased, or fair, as possible. We searched for studies up to May 2017. We assessed the quality of all the studies we included. When it was sensible to do so, we analysed the results of studies together to get an overall result.

Key results

We included 30 studies with 8257 participants. Most of the people in the studies had mild or moderate dementia due to Alzheimer's disease, but in nine studies they had moderate or severe dementia. Almost all of the studies lasted six months or less. The majority of the studies were known to have been funded by the manufacturer of donepezil.

We found that people with Alzheimer's disease who took 10 mg of donepezil a day for six months did slightly better than people taking placebo, on scales measuring their cognitive function (e.g. thinking and remembering), how well they could manage their daily activities, and the overall impression of a trained researcher. We did not find any effect on behaviour or quality of life.

People taking donepezil were more likely than those taking placebo to report side effects and to drop out of the studies. Most side effects were described as mild. Nausea, vomiting and diarrhoea were most common.

Comparing 5 mg of donepezil a day with 10 mg/day, people on 5 mg had fewer side effects, but did slightly less well on cognitive function tests. A higher dose (23 mg/day) offered no advantages and was associated with more side effects.

There is some evidence that use of donepezil is neither more nor less expensive than placebo when total health care costs are taken into account.

Quality of the evidence

In general, we thought that the quality of the evidence was moderate. The main factor reducing our confidence was concern that the results of some studies might have been biased by the way they were done. We cannot be sure that the results apply to treatment longer than six months.

Conclusions

After six months of treatment, there are benefits of donepezil that are large enough to measure in studies. It is associated with side effects that are mainly mild, but that may cause people to stop treatment.

Being able to stabilise cognitive performance or ability to maintain activities of daily living may be important clinically. In terms of total healthcare costs the use of donepezil appears cost neutral. However, there does not appear to be an effect on quality of life. More data are still required from longer-term clinical studies examining measures of disease progression or time to needing full time care.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Donepezil 10 mg/day compared with placebo for dementia due to Alzheimer's disease

Patient or population: people with Alzheimer's disease
Settings: worldwide
Intervention: donepezil 10 mg/day for 24 to 26 weeks
Comparison: placebo for 24 to 26 weeks

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Donepezil 10 mg/day				
Cognitive function (change from baseline at 26 weeks using ADAS-Cog)[1]		The mean score in the donepezil group was 2.67 lower (3.31 to 2.02 lower) than in the placebo group		1130 (5 studies)	⊕⊕⊕◯ **moderate**[2]	ADAS-Cog score has a maximum of 70 points, the lower score in the donepezil group indicates greater improvement
Cognitive function (change from baseline at 26 weeks using MMSE)[1]		The mean score in the donepezil group was 1.05 higher (0.73 to 1.37 higher) than in the placebo group		1757 (7 studies)	⊕⊕⊕◯ **moderate**[2]	MMSE has a maximum score of 30 points, a lower score indicates greater impairment. Treatment effect was in favour of donepezil
Activities of daily living (change from baseline at 26 weeks measured using the ADCS)[1]		The mean score in the intervention group was 1.03 higher (0.21 to 1.85 higher) than in the placebo group		733 (3 studies)	⊕⊕⊕◯ **moderate**[2]	The higher score indicates greater improvement.

Clinician-rated global impression tests (improved compared with baseline, measured using CIBIC-plus at 24-26 weeks)[1]	331 per 1000	487 per 1000 (432 to 542)	**OR 1.92** (1.54 to 2.39)	1674 (6 studies)	⊕⊕⊕◯ **moderate**[2]	
Behavioural symptoms (change from baseline at 26 weeks measured using the NPI)[1]		The mean score in the intervention group was 1.62 lower (3.43 lower to 0.19 higher) than in the placebo group		1035 (4 studies)	⊕⊕⊕◯ **moderate**[2]	A lower score indicates greater improvement. There was no significant difference between the 2 groups
Acceptability of treatment (as measured by withdrawals from trial before end of treatment at 26 weeks)[1]	248 per 1000	291 per 1000 (256 to 331)	**OR 1.25** (1.05 to 1.50)	2846 (12 studies)	⊕⊕⊕◯ **moderate**[2]	Withdrawals were significantly more frequent in the donepezil group compared with placebo group
Incidence of adverse events (at least one adverse event by 26 weeks)[1]	780 per 1000	849 per 1000 (822 to 874)	**OR 1.59** (1.31 to 1.95)	2500 (10 studies)	⊕⊕⊕◯ **moderate**[2]	Adverse events were significantly more frequent in the donepezil group compared with placebo group
Quality of life of participants (change from baseline at 26 weeks)[1]		The mean score was 2. 79 lower (8.15 lower to 2.56 higher) than in the placebo group		815 (2 studies)	⊕⊕⊕◯ **moderate**[2]	A higher svcore indicates greater improvement.There was no significant difference between the 2 groups

*The **assumed risk is the weighted average across studies**. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive; **ADCS**: Alzheimer's Disease Cooperative Study; **CI:** confidence interval; **CIBIC**: Clinician's Interview-Based Impression of Change; **MMSE**: Mini-Mental State Examination; **NPI**: Neuropsychiatric Inventory; **OR:** odds ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]All statistics are based on the analyses of the intention to treat last observation carried forward (ITT-LOCF) population. Although using the ITT population in the analyses for studies in degenerative conditions can be criticised as substitution of the LOCF when a patients is lost before end point may enhance the outcome, in this review the results of the analyses of the population who completed the study were similar to the ITT results and did not alter our conclusions.

[2]Downgraded one level due to the risk of bias due to lack of information on allocation concealment and on the blinding of outcome assessment.

BACKGROUND

Description of the condition

Dementia is a syndrome of acquired deficits in multiple domains of cognition severe enough to interfere with everyday life and not due to impaired consciousness or the effects of a systemic illness (Chertkow 2013). Memory is usually the most severely affected domain initially. Progression is evident as increasing impairment of memory, developing gradually into a global impairment of cognition, including orientation, language, judgement, perceptual ability and praxis (the ability to carry out complex actions). These cognitive impairments are accompanied by progressive deterioration in ability to carry out activities of daily living, and often by the appearance of challenging behaviours and other psychiatric features. The clinical course is associated with growing disability and dependency on carers. A characteristic feature of the disease is a widely variable rate of progression in different patients (Ritchie 2017).

Alzheimer's disease is the most common cause of dementia, and may be involved in as many as 80% of cases. It is a primary degenerative disease of the brain of unknown cause, which leads to dementia of insidious onset, most commonly in later life. The characteristic brain pathology includes progressive loss of neurons and the development in the brain of amyloid plaques and neurofibrillary tangles (Ryan 2015).

This review is an updated version of a review first published in 1998.

Description of the intervention

Donepezil (Aricept, E2020) is a second-generation cholinesterase inhibitor (Lee 2015). The drug was developed by Eisai and received approval from the United States Food and Drug Administration (FDA) in 1996, and from the European Medicines Agency (EMA) in 1997. In most countries it is approved for the treatment of mild or moderate dementia due to Alzheimer's disease. However, in several countries, including the USA, Canada and Japan, it is also approved for use in severe dementia due to Alzheimer's disease. Donepezil is available in tablet form. Liquid and transdermal formulations have also been developed, but are not marketed in all countries. The recommended oral dose is 5 mg once a day initially, increasing to 10 mg once a day after at least one month of treatment. In 2010 the FDA approved a 23 mg, once-a-day tablet of donepezil. Two other cholinesterase inhibitors (rivastigmine and galantamine) are also available.

How the intervention might work

Acetylcholine is an important neurotransmitter associated with memory, and abnormalities in cholinergic neurons (including cell loss) are prominent among the pathological changes in the brains of people with Alzheimer's disease. One approach to lessening the impact of these abnormalities is to inhibit the breakdown of acetylcholine in synapses, thereby enhancing cholinergic neurotransmission. Donepezil does this by reversibly inhibiting the enzyme acetylcholinesterase (Lee 2015).

Why it is important to do this review

Large multicentre studies have been completed. Donepezil has received approval for use in more than 90 countries, including all the member states of the European Union and in the USA. It is important to assess the safety and efficacy of this intervention in a systematic review (Ryan 2015).

OBJECTIVES

To assess the clinical efficacy and safety of donepezil in people with mild, moderate or severe dementia due to Alzheimer's disease; to compare the efficacy and safety of different doses of donepezil; and to assess the effect of donepezil on healthcare resource use and costs.

METHODS

Criteria for considering studies for this review

Types of studies

We included all unconfounded, randomised, double-blind studies of people with dementia due to Alzheimer's disease in which treatment with donepezil was administered for 12 weeks or longer and compared with a placebo group, or in which two doses of donepezil were compared. We excluded studies with a withdrawal design, (i.e. studies in which participants already stable on donepezil treatment were randomised to placebo or continuing donepezil treatment), studies in which the allocation to treatment or control was not randomised, or in which treatment allocation was not concealed. This is because prior knowledge of treatment allocation may lead to biased participant allocation (Schulz 1995).

Types of participants

The participants in studies to be included were diagnosed with probable Alzheimer's disease according to internationally accepted criteria such as ICD-10, the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (APA 1987) and Communicative

Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann 1984).

Types of interventions

Donepezil of any formulation and dose given for at least 12 weeks, compared with placebo or with an alternative formulation or dose of donepezil.

Types of outcome measures

The primary outcomes of interest were as follows.

- Cognitive function (as measured by psychometric tests)
- Activities of daily living
- Behavioural disturbance
- Clinical global impression
- Quality of life
- Effect on carer
- Dependency (such as institutionalisation)
- Death
- Acceptability of treatment as measured by withdrawal from trial
- Safety as measured by the incidence of adverse effects (including side effects) leading to withdrawal
- Safety as measured by the overall incidence of adverse effects
- Direct and indirect costs

We noted physiological outcomes, such as plasma levels, changes on functional imaging or electroencephalogram (EEG) changes but did not assess them, as they are not primarily measures of efficacy.

Search methods for identification of studies

Electronic searches

We identified the studies from a search of ALOIS - Cochrane Dementia and Cognitive Improvement's Specialized Register on 20 May 2017 using the search terms: donepezil, aricept, "E 2020", E-2020 and E2020.

ALOIS is maintained by Cochrane Dementia and Cognitive Improvement's Information Specialist, and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy people. The studies in the Specialized Register are identified from:

- monthly searches of a number of major healthcare databases: MEDLINE, Embase, Cinahl, Psycinfo and Lilacs;
- monthly searches of a number of trials registers: the World Health Organization (WHO) portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
- quarterly searches of The Cochrane Library's Central Register of Controlled Trials (CENTRAL); and
- six-monthly searches of the grey literature source: ISI Web of Science Core Collection

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.

Details of the search strategies used for the retrieval of reports of studies from the healthcare databases, CENTRAL can be viewed in the 'Methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group. The Information Specialist performed additional searches in many of the sources listed above to ensure that the search for the review was as up-to-date and as comprehensive as possible. For a full list of sources searched and view the search strategies used for each source see Appendix 1.

Searching other resources

We performed an additional Internet search using Copernic 2000 on 21 and 22 June 2005 using trial names and numbers. No new studies were found other than the ones that had already been found in the update search of the CDCIG Register on 12 June 2005; we did find additional references to existing studies. We searched Eisai/Pfizer, FDA, EMEA and NICE websites.

Data collection and analysis

Selection of studies

We discarded irrelevant publications, based on the title of the publication and the abstract. In the presence of any suggestion that an article could be relevant, we retrieved it for further assessment. We independently reviewed the studies for inclusion from the culled citation list.

Data extraction and management

One review author (JSB) extracted data from the published reports. The summary statistics required for each trial and each outcome for continuous data were the mean change from baseline, the standard deviation of the mean change, and the number of participants for each treatment group at each assessment. We defined the baseline assessment as the latest available assessment prior to randomisation, but no longer than two months before. Where changes from baseline were not reported, we extracted the mean, standard deviation and the number of participants in each treatment group at each time point if available, and we calculated the required summary statistics. In this case, we assumed a zero correlation between the measurements at baseline and assessment time.

This method overestimates the standard deviation of the change from baseline, but this conservative approach is considered to be preferable in a meta-analysis. The outcomes measured in studies of dementia and cognitive impairment often arise from ordinal rating scales. Where the rating scales used in the studies had a reasonably large number of categories (more than 10) we treated the data as continuous outcomes arising from a normal distribution. For binary data, we sought the number in each treatment group and the numbers experiencing the outcome of interest.

We sought data on every person assessed for each outcome measure. The reported analyses were performed on an intention-to-treat (ITT) basis, which included all participants who were randomised to treatment, assessed at baseline, received at least one dose of the study drug, and had at least one post-baseline assessment. The ITT population consisted of those who provided complete data at endpoint regardless of compliance (the observed cases, OC) plus the LOCF population, (the last observation carried forward on double-blind treatment), for whom the last observation on double-blind treatment was carried forward to endpoint. The study authors analysed these data in the endpoint analyses, which were the primary analyses and are described as ITT-LOCF. To allow a completers' analysis, we sought the data, 'on-treatment' or the data of those who completed the trial, and we indicated them as such.

We did not use data from 'open-label' follow-on phases after the randomised study to assess safety or efficacy.

Assessment of risk of bias in included studies

We conducted the 'Risk of bias' assessment using the standard recommended approach for studies included in Cochrane Reviews (Higgins 2017). The Cochrane Collaboration 'Risk of bias' tool assesses the following domains:

- sequence generation
- allocation concealment
- blinding of participants and study personnel
- blinding of outcomes assessment
- incomplete outcome data
- selective outcome reporting
- other bias

We made a judgement about the risk of bias in each domain, assigning it to one of three categories, high, low, or unclear risk of bias, basing our assessments on the criteria for making judgements that are listed in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). The criteria focus on whether the risk is of importance (that is, whether the presence of the risk could have an important impact on the results of the trial) rather than whether a risk of bias is present or not.

If insufficient detail was reported to make a judgement, we usually considered this as an unclear risk of bias. We also used an 'unclear' judgement in situations where it was clear what happened in the trial but its likely impact on the results was not known.

Measures of treatment effect

For dichotomous outcomes the estimate of treatment effect of the intervention was the Peto odds ratio (OR) together with 95% confidence interval (CI).

For continuous data the measure of treatment effect was the mean difference (MD) if only one study was included, or the weighted mean difference (WMD) if more than one study was included with 95% CI. When the pooled studies used different rating scales to measure the same outcome, then the measure of treatment effect was the standardised mean difference, which is the absolute mean difference divided by the pooled standard deviation.

Unit of analysis issues

The review only included parallel-group studies with individual patients randomised. There were no unit of analysis issues.

Dealing with missing data

We made no attempt at data imputation, except for the estimation of standard deviations for continuous data using the methods detailed in section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Where possible we reported ITT analyses. We conducted sensitivity analyses to compare methods of dealing with missing data.

Assessment of heterogeneity

Before pooling data we assessed potential differences between the included studies in the types of participants, interventions or control used. We did not plan any subgroup analyses.

We assessed heterogeneity between the studies using the Chi^2 test (with a significance level set at $P < 0.10$) and the I^2 statistic (Higgins 2003), which calculates the percentage of variability due to heterogeneity rather than to chance, with I^2 values over 50% suggesting substantial heterogeneity (Deeks 2017).

Assessment of reporting biases

We compared outcomes reported for a trial with its protocol where possible, to examine whether all of the study's pre-specified outcomes had been reported.

Data synthesis

The duration of the studies varied. If we considered the range too great to combine all studies into one meta-analysis, we divided the data into smaller time periods and conducted a separate meta-analysis for each period. Studies could contribute data to more than one time period if they had made multiple assessments.

We have presented overall estimates of the treatment difference. In all cases we have presented the overall estimate from a fixed-effect model and performed tests for heterogeneity using a standard Chi ^{2} statistic and I^2 statistic.

Subgroup analysis and investigation of heterogeneity

We examined heterogeneity both visually and using the I^2 statistic (Deeks 2017).

Sensitivity analysis

This review sought to analyse data using ITT data wherever possible. Some studies reported both an ITT analysis that included all participants randomised and a per protocol analysis. The ITT analyses often involve data imputation techniques such as LOCF for participants who did not complete the study. We investigated the impact of different ways of dealing with missing data using a sensitivity analysis of ITT and per protocol analyses. We tabulated these results and discussed any important discrepancies.

Presentation of results: 'Summary of findings' table

We used the GRADE approach (Guyatt 2011) to describe our confidence in key effect estimates and presented them in 'Summary of findings' tables as recommended by Cochrane (Schünemann 2017). The GRADE approach rates the overall quality of evidence contributing to an effect estimate as high, moderate, low or very low, taking into account risk of bias in the included studies, inconsistency between studies, imprecision in the effect estimate, indirectness with respect to the review question, and possible publication bias. We produced 'Summary of findings' tables for the comparison of donepezil (10 mg/day) versus placebo, for the comparison of donepezil (10 mg/day) versus donepezil (5 mg/day), for the comparison of donepezil (10 mg/day) versus placebo for severe Alzheimer's disease, and for the comparison of donepezil (10 mg/day) versus donepezil (23 mg/day). We included the following key outcomes in the 'Summary of findings' tables: cognitive function, activities of daily living, behavioural symptoms, clinician-rated global impression, acceptability of treatment, incidence of adverse events and quality of life.

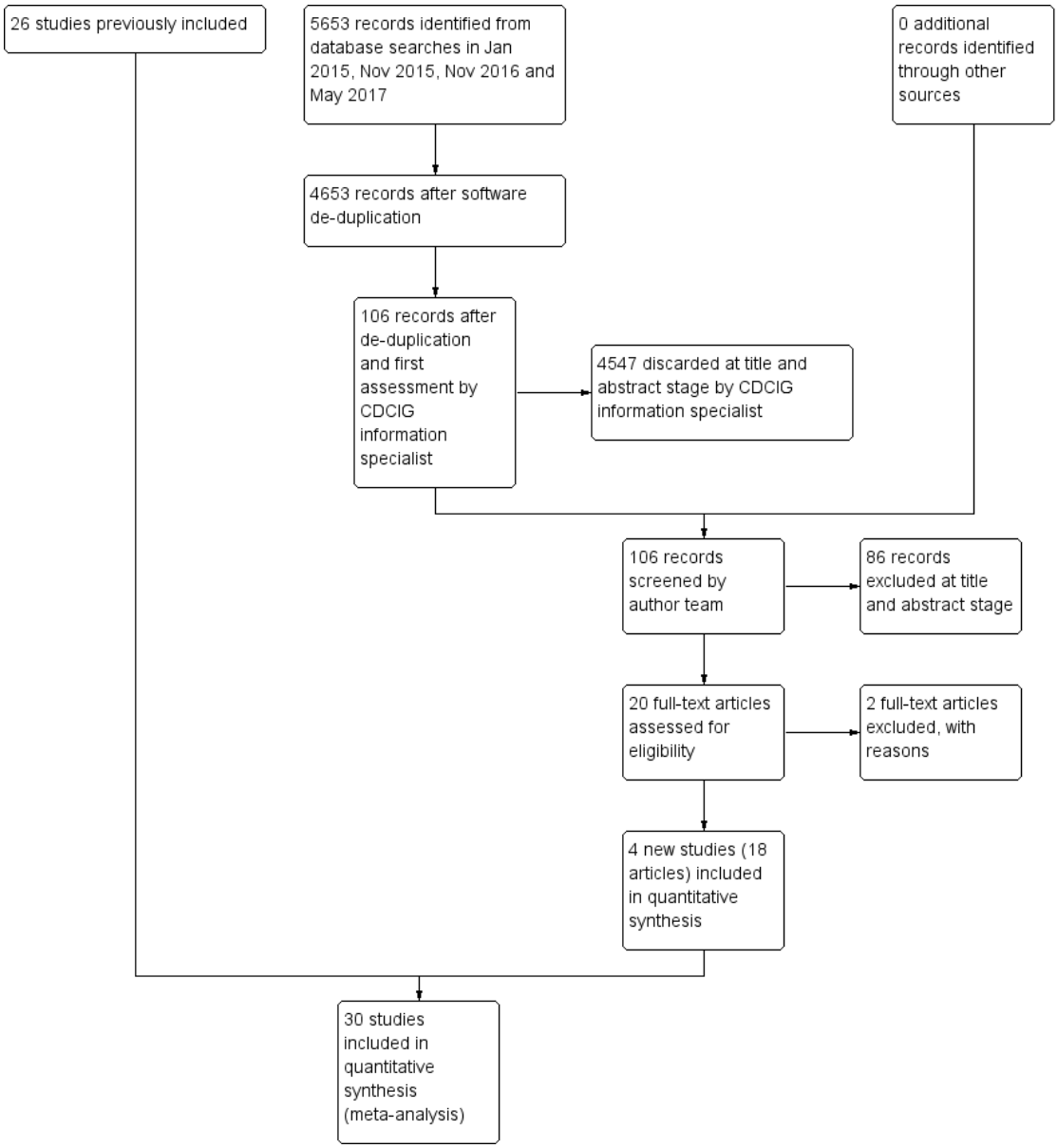
RESULTS

Description of studies

Results of the search

The updated searches performed in January 2015, November 2015, November 2016 and May 2017 retrieved a total of 5653 references. After de-dulication and a first assessment based on titles and abstracts by the CDCIG information specialist, we were left with 106 references. We read the full texts of 16 references from the January and November 2015 searches. Of these, 14 references were related to two studies suitable for inclusion, and two reported studies that we excluded. From the other two searches, November 2016 and May 2017, we read the full texts of four references. Of these, two were additional references for studies already included, and two were new studies to be included, see Figure 1.

Figure 1. Study flow diagram for searches conducted in January 2015, November 2016 and May 2017



Included studies

We have summarised the characteristics of the 30 included studies in Characteristics of included studies.

We have summarised Important details of study design (number of participants, duration of follow-up, mean Mini-Mental State Examination (MMSE) of participants at baseline and description of interventions) in Table 1, the outcome measures in Table 2, and the objectives of the studies in Table 3.

Design, participants, sample sizes and interventions

Only randomised, double-blind, placebo-controlled studies, or studies comparing different doses of donepezil were included in this review. All included studies were described as randomised and double-blind, but further details on the randomisation and blinding were not always reported.

All included studies have been reported since 1996.

Studies published in 2001 or earlier

Eleven studies were reported in 2001 or earlier.

Of these, six studies (Homma 1998; Rogers 1996; Rogers 1998a; Rogers 1998b; Burns 1999; Winblad 2001) were designed to evaluate the efficacy and safety of donepezil in people with mild to moderately severe dementia due to Alzheimer's disease and one study (Tariot 2001), was designed to examine efficacy, safety and tolerability in the management of very elderly residents with Alzheimer's disease in nursing homes, particularly the effect of donepezil on neuropsychiatric manifestations. Rogers 1996, Rogers 1998a, Rogers 1998b, Burns 1999 and Tariot 2001 were all supported by Eisai Inc. The Winblad 2001 was supported by Pfizer Inc. It is not clear how Homma 1998 was supported. Rogers 1996 was described as a phase II study, and Rogers 1998a, Rogers 1998b, Burns 1999 and Tariot 2001 as phase III studies.

These studies had many features in common. They were all multicentre, parallel-group studies. Four studies were based in the USA, two in Europe and one in Japan. All studies compared donepezil with placebo.

These seven studies made a diagnosis for probable Alzheimer's disease according to NINCDS-ADRDA criteria, with participants also fitting DSM-III-R illness categories 290.00 or 290.10 in six studies. Rogers 1996, Rogers 1998a, Rogers 1998b, Burns 1999 and the Winblad 2001 measured the severity of the disease using the MMSE scale, and recruited participants with mild to moderate dementia (MMSE 10-26). Tariot 2001 recruited participants with MMSE between 5 and 26, inclusive, and consequently the mean MMSE at baseline (14.4) was lower than that in the other studies. Homma 1998 did not use the MMSE. Homma 1998, Rogers 1996, Rogers 1998a, Rogers 1998b, and Burns 1999 required a Clinical Dementia Rating (CDR) of 1 (mild) or 2 (moderate) at screening and baseline.

The list of exclusions was quite extensive and consistent across the phase II and III studies. Patients were excluded if they had insulin-dependent diabetes mellitus or other endocrine disorder, asthma, obstructive pulmonary disease or clinically significant uncontrolled gastrointestinal hepatic or cardiovascular diseases. Patients known to be hypersensitive to cholinesterase inhibitors or who had taken tacrine or other investigational medicines within one month of baseline were excluded. Concomitant medications such as anticholinergics, anticonvulsants, antidepressants and antipsychotics were not allowed. Drugs with central nervous system (CNS) activity were prohibited or partially restricted. The participants included in Tariot 2001 were on average older than in the other studies, and were more likely to have comorbid illness. They were required to have reported at a frequency of several times a week at least one symptom from the Neuropsychiatric Inventory Nursing Home version (NPI-NH).

The Winblad 2001 published an economic valuation of donepezil.

The doses used in the phase III studies were within the range shown to be clinically useful and reasonably well tolerated in the earlier studies. Treatment was once daily. When the dose of donepezil was 5 mg/day or less, the participants began with the full dose; with 10 mg/day the initial dose was 5 mg/day for one week followed by the full dose for Rogers 1998a, Rogers 1998b and Burns 1999. For the two later studies, Tariot 2001 and the Winblad 2001, the time on 5 mg/day was four weeks, before increasing to 10 mg/day. The forced titration schemes were blinded. Homma 1998 and Rogers 1996 were dose-finding studies.

Four other studies were published in 2001 or before (Lebert 1999; Feldman 2001; Homma 2000; Mohs 2001).

Lebert 1999 was a large, multi-centred trial designed to evaluate the stress on carers.

Homma 2000 was a multicentre, phase III study carried out in Japan, funded by Eisai, with a similar protocol to the other Eisai phase III studies, except that only the lower dose of donepezil, 5 mg/day was tested and participants began with a lower dose for the first week.

Mohs 2001 investigated the effect of donepezil on the preservation of function over a one-year period. The inclusion and exclusion criteria were similar to the phase III studies, except for baseline MMSE, which was approximately 5 points lower on average, and for the requirement that participants had to be able to perform eight of 10 instrumental activities of daily living and five of six basic activities of daily living, each scored on a scale of 0 (no impairment) to 3 (very severe impairment) to a level no greater than 2. The primary endpoint was time to clinically evident decline in function, as defined in the protocol. Participants reaching this

endpoint left the trial and received open-label donepezil treatment. It was not possible to include the results of this trial in the meta-analyses due to the removal of participants from the study. The only outcome we could include was the number in each group reaching the primary endpoint.

Feldman 2001 recruited patients with probable or possible Alzheimer's disease of moderate to severe severity. Causes of the dementia, other than Alzheimer's disease, had to be ruled out. Patients randomised to donepezil took 5 mg/day for 4 weeks, followed by 10 mg/day for 20 weeks if the higher dose was tolerated. The trial was supported by Pfizer Inc and Eisai Co Ltd. An economic evaluation of donepezil from Feldman 2001 has been published. Data were collected at four time points, including baseline, during the randomised treatment period, on patient and carer health resource utilisation and costs. Details are described below.

Studies published after 2001

The remaining 19 included studies were reported after 2001.

Tune 2003, with only 28 participants, was primarily aimed at investigating brain glucose metabolism; Study 205, with 12 participants investigated the effect on visuospatial attention and Study 306, with 39 participants, investigated whether Apo E genotype predicted response to donepezil. Krishnan 2003, with 67 participants, was primarily to investigate brain measurements. There is very little published information on these studies.

AD2000 randomised 566 people with Alzheimer's disease, with or without vascular dementia, to 12 weeks of 5 mg/day donepezil or placebo, and then re-randomised them to donepezil (5 mg/day or 10 mg/day) or placebo for another 48 weeks of treatment. Thus the trial was partially of a cross-over design, some participants changed treatments, others did not. In addition, suitable participants were randomised to aspirin or aspirin avoidance. This trial was carried out independently of the pharmaceutical company. An extensive description of and the results from AD2000 have been published. The trial was designed with the intention of recruiting 3000 people, but only 566 were randomised. When this UK-based trial started in 2000 donepezil was not available on the National Health Service (NHS), but became available in 2001. This affected not only recruitment, but also the retention of participants because participants already randomised left the trial to benefit from open-label prescription of donepezil. Any patient referred to a memory clinic was potentially eligible if they were diagnosed (according to DSM IV) with dementia of Alzheimer type with or without a coexisting diagnosis of vascular dementia (16% of participants were also diagnosed with vascular dementia). Only 86% (486/566) of participants randomised at baseline entered the second randomisation at 12 weeks. During the next 48 weeks of treatment 40% (193) of participants were lost to follow-up, 32 died, 42 were admitted to institutional care, 62 stopped treatment and 57 withdrew to open-label donepezil. The trial continued with a six-week washout before beginning a further 48 weeks of treatment (no further randomisation), but only 194 out of 293 finishing the previous phase entered. After the second 48-week phase there was a four-week washout, another 48 weeks of treatment, four-week washout and 48 weeks of treatment. In theory, treatment could continue for 204 weeks, but the loss of participants continued at a substantial rate. The two primary endpoints were entry to an institution, and loss of either two of four basic, or six of 11 instrumental activities on the BADLS. Secondary outcome measures were functional ability (BADLS), behavioural symptoms as assessed by the NPI, MMSE, psychological well-being of the carer (GHQ-30), and death from Alzheimer's disease. In addition, AD2000 assessed costs, including NHS, social services and private, from information provided by the carer and by the family doctor, and costed using national (UK) average unit costs for each item, for example a stay in hospital.

Hegerl 2003 was a small pilot study of 40 participants diagnosed with probable Alzheimer's disease according to DSM-IV and NINCDS-ADRDA, designed to investigate whether donepezil is associated with Parkinsonian effects in people with Alzheimer's disease, by assessing cognition and hand-motor function. It was supported by Pfizer Inc. and Eisai Europe.

Schindler 2004 was a small study of 31 participants with mild to moderate Alzheimer's disease, who were already taking 10 mg/day donepezil at baseline. The objective was to assess the safety and tolerability of higher doses of donepezil. In addition to the 10 mg/day that the participants were already taking, participants were randomised to either placebo or to a further dose of 5 mg /day increasing to 10 mg/day donepezil over 24 weeks. It was funded by Pfizer/Eisai.

Seltzer 2004, a 24-week, parallel-group study of 10 mg/day donepezil compared with placebo, evaluated the efficacy of donepezil in participants with early-stage Alzheimer's disease. The mean MMSE at baseline was 24.

Winblad 2006, a placebo-controlled, six-month study conducted in Sweden and funded by Pfizer, was designed to investigate the efficacy of donepezil in people with severe Alzheimer's disease. The 241 participants were living in assisted-care nursing homes. Their baseline MMSE was between 1 and 10 points. Participants were randomised to donepezil (5 mg/day for 30 days followed by up to 10 mg/day) or placebo. The primary outcomes were cognition, as assessed by the SIB, and activities of daily living.

Black 2007, a placebo-controlled, 24-week study conducted in Australia, Canada, France, the UK and the USA, and funded by Pfizer, was designed to investigate the efficacy of donepezil in people with severe Alzheimer's disease. The 343 participants were living in the community or in assisted-care nursing homes. Their baseline MMSE was between 1 and 12 points. Participants were randomised to donepezil (5 mg/day for six weeks followed by up to 10 mg/day) or placebo. The primary outcomes were cognition as assessed by the SIB and CIBIC-Plus.

Homma 2008, sponsored by Eisai Ltd. Japan, was a placebo-controlled, 24-week trial to investigate two doses of donepezil, 5 mg/

day and 10 mg/day, in Japanese people with severe Alzheimer's disease.

Howard 2007, sponsored by the Medical Research Council (MRC) UK, and the Alzheimer Society, was a placebo-controlled, 12-week trial of 10 mg/day donepezil, for people with severe Alzheimer's disease and significant agitation, a subgroup of the population of people with severe Alzheimer's disease.

Mazza 2006 was a small, 24-week trial, not industry-sponsored, designed to compare *Ginkgo biloba* with donepezil and placebo in mild to moderate Alzheimer's disease. They reported only some of the results.

Moraes 2006a was a small, 12-week trial of people with sleep apnoea and Alzheimer's disease, investigating the effect of donepezil on polysomnography outcomes. Cognition was a secondary outcome.

Moraes 2006b was a small, 26-week trial studying the effect of donepezil on rapid eye movement (REM) sleep in Alzheimer's disease, with cognition as a secondary outcome.

Maher-Edwards 2011 was a small, exploratory study (n = 130) of 24 weeks' duration with three treatment arms, donepezil (10 mg/day), SB-742457 and placebo.

Farlow 2010 and Homma 2016 were parallel-group studies of 24 weeks' duration designed to compare donepezil (10 mg/day) with a slow-release formulation of donepezil (23 mg/day).

Jia 2017, sponsored by Eisai China was a placebo-controlled, 24-week trial to investigate donepezil, 10 mg/day, in Chinese people with severe Alzheimer's disease.

Outcomes

The studies examined cognition, functional and behavioural symptoms, and global effects, as well as the safety and tolerability of donepezil. Apart from the outcomes related to safety or adverse effects, the included studies measured all the outcomes for the effectiveness of donepezil by questionnaires or psychometric tests and used different types of instruments to measure each outcome. We have summarised the details of the outcomes measured and reported in each trial in Table 2.

In all studies assessments were carried out at more than one time point between the base line assessment and the reported end-point. Details of adverse events were ascertained by the questioning of each patient at each assessment. Serious adverse events were reported immediately.

Excluded studies

These are listed in Characteristics of excluded studies. We excluded the greatest number of studies because the control was another drug and not placebo, or because the study was open label.

Risk of bias in included studies

Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

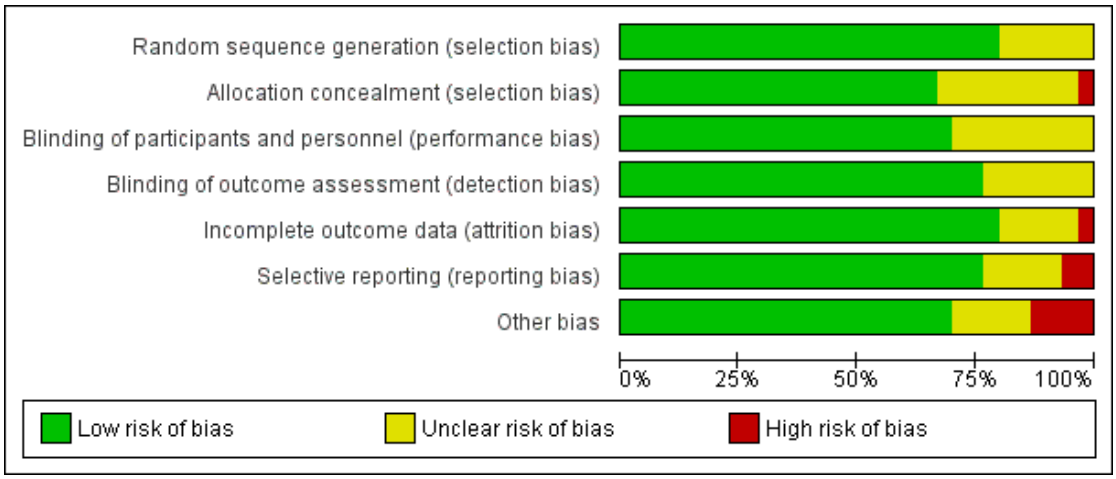
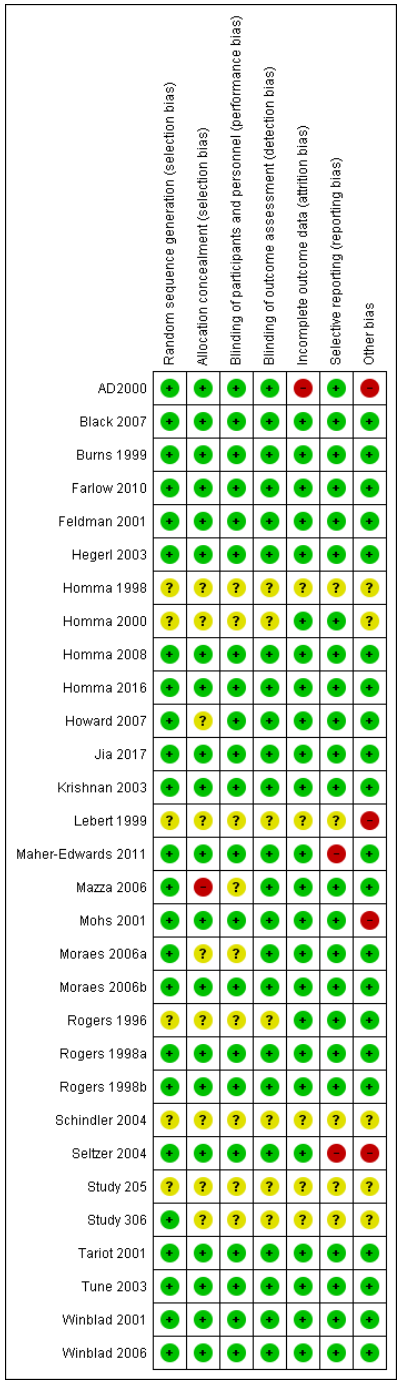


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

We considered all studies sponsored by Eisai Inc. and Pfizer Inc. to be at low risk of bias for randomisation and allocation concealment. Of the independent studies, most had a low risk of bias with clearly described procedures.

Blinding

We considered most studies to be at low risk of bias. All studies were described as double-blinded and were either placebo-controlled or compared different doses of donepezil. Most studies described the interventions as having identical appearance and taste. Nearly all studies described a computer-generated randomisation process, and most studies described the placebo and interventions as having identical appearance and taste, but only six studies described the blinding of the assessors.

Incomplete outcome data

We considered most studies to be at low risk of bias.The number of dropouts was usually small, that is, less than 20%, except for Mohs 2001, and AD2000.

The primary endpoint for Mohs 2001 was time to clinically evident decline in function, as defined in the protocol. Participants reaching this endpoint left the trial and received open-label donepezil treatment. It was not possible to include most of the results of this trial in the meta-analyses owing to the withdrawal of participants. It was possible to consider the time to clinically evident decline in function, but other outcomes would be biased by the risk of differential dropout related to treatment allocation. In order to compare the different methods of dealing with missing assessments, we conducted meta analyses where possible on two populations of participants, the ITT population and the completers' population in order to compare the results. The results from the analyses of the completers' population did not cause us to change our conclusions.

Selective reporting

We considered most studies to be at low risk of bias.Twenty-three of the 30 included studies reported all outcomes according to the outcomes identified in the methods section. There was insufficient information to assess the risk in the other seven studies.

Other potential sources of bias

We considered some studies to be at high risk of bias.There are serious concerns about the methodological quality of Lebert 1999. There is limited information available as this trial has never been published except in conference proceedings. These proceedings report that five participants took the wrong treatment.

Participants were withdrawn from Mohs 2001 if they met criteria of clinically evident decline in functional status.

Participants were withdrawn from Seltzer 2004 if they could not tolerate the 10 mg dose.

Effects of interventions

See: **Summary of findings for the main comparison** Donepezil 10 mg/day compared with placebo for dementia due to Alzheimer's disease; **Summary of findings 2** Donepezil 23 mg/day compared with donepezil 10 mg/day for dementia due to Alzheimer's disease; **Summary of findings 3** Donepezil 10 mg/day compared with donepezil 5 mg/day for dementia due to Alzheimer's disease; **Summary of findings 4** Donepezil 10 mg/day compared with placebo for people with severe dementia due to Alzheimer's disease

There are 30 included studies, 21 of which reported results in sufficient detail for analysis. Nine studies contributed limited data or no data. Krishnan 2003 , Study 205, Mazza 2006, Moraes 2006a, Moraes 2006b contributed a tiny amount of data or no data . Detailed results have been published from AD2000 but few are reported in this review as they are difficult to interpret due to the second randomisation three months after baseline, and the high percentage of participants leaving the trial early. Extraction for the meta-analyses and interpretation of the published results is not straight forward due to the complex design of the study and the form in which results were reported. The results from Lebert 1999 and Hegerl 2003 were not published with sufficient detail to allow extraction of the data for the meta-analyses. We have serious concerns about the methodological quality of Lebert 1999. Schindler 2004 published data on the number of adverse events only.

The older studies included participants with mild to moderate Alzheimer's disease, mean baseline MMSE ranging from 17 to 22, but more recent studies have been including participants with more severe Alzheimer's disease. Tariot 2001, Black 2007, Feldman 2001, Homma 2008, Howard 2007, Jia 2017 and Winblad 2006 have mean baseline MMSE ranging from 6 to 14. We have reported the results of Howard 2007 separately, as the included participants were suffering with severe agitation, and thus were a subset of the total population of people with severe Alzheimer's disease. We have combined the results of the other studies with studies of the mild to moderate group and, in addition, we reported separately the results of Black 2007, Feldman 2001, Homma 2008, Howard 2007, Jia 2017 and Winblad 2006, the six studies that included only participants with severe or moderately severe dementia.

We have reported the main objective of each study in Table 3. Nineteen studies examined the cognitive, functional and global

effects of donepezil. We analysed the results for treatment groups taking 5 mg/day and 10 mg/day of donepezil separately. Phase II dose-finding studies had also used doses less than 5 mg/day, but donepezil is not prescribed at less than 5 mg/day and therefore we did not carry out meta-analyses for the treatment groups where dose was less than 5 mg/day.

We analysed results after treatment periods of 12, 24 to 26, and 52 weeks separately.

Where data are available we have reported meta-analyses on the ITT population, where LOCF assessments were incorporated when assessments were missing, and on the completers' population. The results appear similar, suggesting no differential dropout between the treatment groups. Models were fitted using fixed effects. There is evidence of heterogeneity between the studies for a few meta-analyses. We rated outcomes as moderate quality, downgraded one level due to the risk of bias due to lack of information on allocation concealment and on the blinding of outcome assessment for some of the studies. Twenty-two of the 30 studies did not describe allocation concealment and blinding of outcome, and 17 of the 30 studies did not describe blinding of the intervention.

The rating scales and cognitive tests differ in the direction representing improvement, or fewer symptoms:

- a decrease in score indicates improvement with the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog), Activities of Daily Living (ADL), Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), Clinical Dementia Rating scale (CDR), Clinician's Interview-Based Impression of Change scale (CIBIC-Plus), Cohen-Mansfield Agitation Inventory (CMAI), Chrichton Scale (CMCS), Gottfries, Brane and Steen scale (GBS), Neuropsychiatric Instrument (NPI), Neuropsychiatric Inventory Distress scale (NPI-D), and Syndrom Kurz Test (SKT);
- an increase in score shows improvement for the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (severe version) (ADCS-ADL-sev), Disability Assessment for Dementia (DAD), Mini Mental State Examination (MMSE), Progressive Deterioration Scale (PDS), Quality of Life scale (QoL), and Severe Impairment Battery (SIB). (See Appendix 2 for more information about tests and rating scales.)

Comparison of donepezil (10 mg/day) with placebo

Cognitive function

The meta-analysis, using mean differences (MDs) revealed a benefit on cognitive function as measured by the ADAS-Cog test score for donepezil compared with placebo at 24 to 26 weeks (MD -2.67 , 95% CI -3.31 to -2.02, P < 0.00001, 5 studies, 1130 participants, ITT analysis; Analysis 1.1).

The MMSE showed similar results in favour of donepezil at 24 to 26 weeks compared with placebo (MD 1.05, 95% CI 0.73 to 1.37, P < 0.00001, 7 studies, 1757 participants, ITT analysis; Analysis 1.2).

The SIB showed similar results in favour of donepezil at 24 to 26 weeks compared with placebo (MD 5.92, 95% CI 4.53 to 7.31, P < 0.00001, 5 studies, 1348 participants, ITT analysis; Analysis 1.3).

Activities of daily living

The meta-analysis, using MDs revealed a benefit on activities of daily living as measured by the ADCS-ADL-sev test score for donepezil compared with placebo at 24 to 26 weeks (MD 1.03 , 95% CI 0.21 to 1.85, P = 0.01, 3 studies, 733 participants, ITT analysis; Analysis 1.4).

Global assessment

We dichotomised the seven-point CIBIC-Plus scale, or the Clinician's Global Impression of Change (CGIC) by counting those showing no change or decline against those showing improvement. There was benefit associated with donepezil (276/834), compared with placebo (173/840), at 24 to 26 weeks (OR 1.92, 95% CI 1.54 to 2.39, P < 0.00001, 6 studies, 1674 participants, ITT analysis; Analysis 1.5).

We also used mean differences to analyse the CDR sum of boxes, measuring both cognitive function and aspects of everyday functioning together in a single score. It shows a benefit for donepezil compared with placebo at 24 to 26 weeks, (MD -0.53, 95% CI -0.73 to -0.33, P < 0.00001, 3 studies, 1028 participants, ITT analysis; Analysis 1.6).

Behavioural symptoms

Four studies (MD -1.62, 95% CI -3.43 to 0.19, P = 0.08, 4 studies, 1035 participants, ITT analysis; Analysis 1.8), assessed behavioural symptoms using the NPI, and one study (MD 0.40, 95% CI -1.28 to 2.08, P = 0.64, 194 participants, ITT analysis; Analysis 1.7) using the BEHAVE-AD score. There was no difference between donepezil and placebo at 24 to 26 weeks for either score.

Withdrawals before the end of treatment

The meta-analysis of withdrawals before the end of treatment showed a benefit in favour of placebo (282/1401) compared with donepezil (348/1445) at 24 to 26 weeks (OR 1.25, 95% CI 1.05 to 1.50, P = 0.0013, 12 studies, 2846 participants, ITT analysis; Analysis 1.10).

Adverse events

The meta-analysis of numbers of participants with at least one adverse event before the end of treatment showed a benefit in favour of placebo (793/1226) compared with donepezil (913/1274) at 24 to 26 weeks (OR 1.59, 95% CI 1.31 to 1.95, P < 0.00001, 10 studies, 2500 participants, ITT analysis; Analysis 1.11).

Quality of life

The meta-analysis, using MDs showed no difference for QoL between donepezil 10 mg/day compared with placebo at 24 weeks (MD -2.79, 95% CI -8.15 to 2.56, P = 0.31, 2 studies, 815 participants, ITT analysis; Analysis 1.9).

Comparison of donepezil (5 mg/day and 10 mg/day) with placebo

Cognitive function

The meta-analyses, using MDs, revealed a benefit on cognitive function as measured by ADAS-Cog test scores for the lower-dose and higher-dose donepezil compared with placebo at 12, and 24 to 26 weeks.

- 5 mg/day donepezil at 12 weeks (MD -2.27, 95% CI -3.16 to -1.39, P < 0.00001, 3 studies, 488 participants, ITT analysis; Analysis 2.2)
- 10 mg/day donepezil at 12 weeks (MD -2.99, 95% CI -3.99 to -1.99, P < 0.00001, 5 studies, 459 participants, ITT analysis; Analysis 2.2)
- 5 mg/day donepezil at 24 weeks (MD -2.01, 95% CI -2.69 to -1.34, P < 0.00001, 3 studies, 1089 participants, ITT analysis; Analysis 2.2)
- 10 mg/day donepezil at 24 weeks (MD -2.67, 95% CI -3.31 to -2.02, P < 0.00001, 5 studies, 1130 participants, ITT analysis; Analysis 2.2)

The MMSE showed similar results in favour of the lower-dose and higher-dose donepezil compared with placebo at 12, 24 to 26, and 52 weeks.

- 5 mg/day donepezil at 12 weeks (MD 0.92, 95% CI 0.32 to 1.53, P = 0.003, 2 studies, 382 participants, ITT analysis; Analysis 2.4)
- 10 mg/day donepezil at 12 weeks (MD 1.19, 95% CI 0.61 to 1.77, P < 0.0001, 2 studies, 511 participants, ITT analysis; Analysis 2.4)
- 5 mg/day donepezil at 24 weeks (MD 1.22, 95% CI 0.54 to 1.90, P = 0.0004, 2 studies, 358 participants, ITT analysis; Analysis 2.4)
- 10 mg/day donepezil at 24 weeks (MD 1.05, 95% CI 0.73 to 1.37, P < 0.000001, 7 studies, 1757 participants, ITT analysis; Analysis 2.4)
- 10 mg/day donepezil at 52 weeks (MD 1.70, 95% CI 0.81 to 2.59, P = 0.0002, 1 study, 272 participants, ITT analysis; Analysis 2.4)

The meta-analyses, using MDs, revealed a benefit on cognitive function as measured by SIB test scores for the lower-dose and higher-dose donepezil compared with placebo at 24 to 26 weeks.

- 5 mg/day donepezil at 24 weeks (MD 6.70, 95% CI 3.66 to 9.74, P < 0.0001, 1 study, 198 participants, ITT analysis; Analysis 2.5)
- 10 mg/day donepezil at 24 weeks (MD 5.92, 95% CI 4.53 to 7.31, P < 0.000001, 5 studies, 1348 participants, ITT analysis; Analysis 2.5)

Activities of daily living

The Winblad 2001 was the only study to assess activities of daily living using the PDS scale. 10 mg/day donepezil showed benefit compared with placebo at 52 weeks (MD 3.80, 95% CI 1.70 to 5.90, P = 0.0004, 1 study, 276 participants, ITT analysis; Analysis 2.15).

Two other studies assessed activities of daily living, Feldman 2001 (using the DAD, Instrumental ADL and Physical Self-maintenance Scale (PSMS)) and Homma 2000 (CMCS). There was evidence of benefit of donepezil at 12 and 24 weeks.

- 5 mg/day donepezil at 24 weeks (completers' analysis, MD -2.42, 95% CI -4.32 to -0.52, P = 0.01, 1 study, 228 participants, Analysis 2.12) (CMCS)
- 10 mg/day donepezil at 12 weeks (completers' analysis, MD 4.83, 95% CI 1.35 to 8.31, P = 0.007, 1 study, 254 participants, Analysis 2.13) (DAD)
- 10 mg/day donepezil at 24 weeks (completers' analysis, MD 8.00, 95% CI 3.61 to 12.39, P = 0.0004, 1 study, 247 participants, Analysis 2.13) (DAD)
- 10 mg/day donepezil at 12 weeks (completers' analysis, MD -4.31, 95% CI -7.72 to -0.90, P = 0.01, 1 study, 250 participants, Analysis 2.22) (IADL)
- 10 mg/day donepezil at 24 weeks (completers' analysis, MD -6.32, 95% CI -10.02 to -2.62, P = 0.0008, 1 study, 243 participants, Analysis 2.22) (IADL)

Winblad 2006, Homma 2008 and Black 2007 used the ADCS-ADL-severe scale. There was evidence of benefit of donepezil. 10 mg/day donepezil at 24 weeks (MD 1.03, 95% CI 0.21 to 1.85, P = 0.01, 3 studies, 733 participants, ITT analysis; Analysis 2.14).

The primary endpoint of Mohs 2001 was time to clinically evident decline in function, as defined in the protocol. There was evidence of benefit of donepezil 10 mg/day (84/207) compared with placebo (116/206) at 54 weeks (OR 0.53, 95% CI 0.36 to 0.78, P = 0.001, 1 study, 413 participants; Analysis 2.16).

Global assessment

We dichotomised the seven-point CIBIC-Plus scale, measuring global clinical state, counting those showing no change or decline, against those showing improvement, and we analysed the results using the OR. There are benefits associated with 5 mg/day and 10 mg/day donepezil compared with placebo at 12, and 24 to 26 weeks, as shown by the ITT analyses.

- 5 mg/day donepezil at 12 weeks (49/153 donepezil, 27/150 placebo) (OR 2.10, 95% CI 1.25 to 3.53, P = 0.005, 1 study, 303 participants, ITT analysis; Analysis 2.7)
- 10 mg/day donepezil at 12 weeks (58/152 donepezil, 27/150 placebo) (OR 2.70, 95% CI 1.64 to 4.46, P = 0.0001, 1 study, 302 participants, ITT analysis; Analysis 2.7)
- 5 mg/day donepezil at 24 weeks (187/633 donepezil, 102/640 placebo) (OR 2.20, 95% CI 1.69 to 2.87, P < 0.00001, 4 studies, 1273 participants, ITT analysis; Analysis 2.7)
- 10 mg/day donepezil at 24 weeks (276/834 donepezil, 173/840 placebo) (OR 1.92, 95% CI 1.54 to 2.39, P < 0.00001, 6 studies, 1674 participants, ITT analysis; Analysis 2.7)

The GBS and Mental Function Impairment Scale (MENFIS) are both global assessment scales. Only two studies used these scales, the Winblad 2001 used the GBS and Homma 2000 used the MENFIS. There was some evidence of benefit associated with donepezil (completers).

- 5 mg/day donepezil at 24 weeks (completers, MD -2.56, 95%CI -4.27 to -0.85, P = 0.003, 1 study, 228 participants, Analysis 2.10)
- 10 mg/day donepezil at 52 weeks (completers, MD -6.01, 95%CI -11.93 to -0.09, P = 0.05, 1 study, 190 participants, Analysis 2.10)

We also analysed the CDR-SB using MDs. This measures both cognitive function and aspects of everyday functioning together in a single score, and showed a benefit with 5 mg/day and 10 mg/day of donepezil compared with placebo at 12 weeks, and 10 mg/day of donepezil compared with placebo at 24 weeks, but there was no difference between donepezil 5 mg/day and placebo at 12 weeks.

- 5 mg/day donepezil at 12 weeks (MD -0.02, 95% CI -0.25 to 0.21, P = 0.86, 3 studies, 487 participants, ITT analysis; Analysis 2.9)
- 10 mg/day donepezil at 12 weeks (MD -0.23, 95% CI -0.47 to 0.00, P = 0.05, 4 studies, 559 participants, ITT analysis; Analysis 2.9)
- 5 mg/day donepezil at 24 weeks (MD -0.51, 95% CI -0.70 to -0.32, P < 0.00001, 3 studies, 1093 participants, ITT analysis; Analysis 2.9)
- 10 mg/day donepezil at 24 weeks (MD -0.53, 95% CI -0.73 to -0.33, P < 0.00001, 3 studies, 1028 participants, ITT analysis; Analysis 2.9)

Behavioural symptoms

Feldman 2001, Tune 2003, Winblad 2006, Black 2007 and Tariot 2001 assessed behavioural disturbance (NPI-TOTAL), and there was no evidence of benefit.

- 10 mg/day donepezil at 12 weeks (MD -1.45, 95% CI -4.43 to 1.53, P = 0.34, 2 studies, 279 participants, ITT analysis; Analysis 2.17)
- 10 mg/day donepezil at 24 weeks (MD -1.04, 95% CI -3.16 to 1.07, P = 0.33, 4 studies, 692 participants, ITT analysis; Analysis 2.17)

Homma 2008 assessed BEHAVE-AD and there was no evidence of benefit of donepezil.

- 5 mg/day donepezil at 24 weeks (MD 0.00, 95% CI -1.67 to 1.67, P = 1.0, 1 study, 198 participants, ITT analysis; Analysis 2.18)
- 10 mg/day donepezil at 24 weeks (MD 0.40, 95% CI -1.28 to 2.08, P = 0.64, 1 study, 194 participants, ITT analysis; Analysis 2.18)

Withdrawals before the end of treatment

Donepezil was judged to be fairly well tolerated. The meta-analyses of withdrawals before the end of treatment, using the OR, showed benefit in withdrawals between the 5 mg/day group and the placebo group at 12 weeks in favour of placebo but not at 24 weeks, and for the 10 mg/day group at 12 and 24 weeks in favour of placebo but not at 52 weeks.

- 5 mg/day donepezil at 12 weeks (70/543 donepezil, 40/536 placebo) (OR 1.81, 95% CI 1.22 to 2.68, P = 0.003, 4 studies, 1079 participants, ITT analysis; Analysis 2.26)
- 10 mg/day at 12 weeks (29/184 donepezil, 13/178 placebo) (OR 2.31, 95% CI 1.21 to 4.40, P = 0.01, 2 studies, 362 participants, ITT analysis; Analysis 2.26)
- 10 mg/day donepezil at 24 to 26 weeks (348/1445 donepezil, 282/1401 placebo) (OR 1.25, 95% CI 1.05 to 1.50, P = 0.013, 12 studies, 2846 participants, ITT analysis; Analysis 2.26).
- 10 mg/day donepezil at 52 week (47/142 donepezil, 47/144 placebo) (OR 1.02, 95% CI 0.62 to 1.67, P = 0.93, 1 study, 286 participants, ITT analysis; Analysis 2.26)

Dependency

Feldman 2001 assessed the time spent each day by the carer assisting with the activities of daily living but there was no evidence of a treatment effect. 10 mg/day donepezil at 24 weeks (MD -52.4, 95% CI -118.78 to 13.98, P = 0.12, 1 study, 221 participants, ITT analysis; Analysis 2.24).

Withdrawals before the end of treatment due to adverse events

The meta-analyses of withdrawals before the end of treatment due to adverse events, using the OR, showed differences in withdrawals between the 5 mg/day group and the placebo group at 12 weeks but not at 24 weeks, and for the 10 mg/day group at 12, and 24 to 26 weeks, but not at 52 weeks in favour of placebo.

- 5 mg/day donepezil at 12 weeks (17/260 donepezil, 7/253 placebo) (OR 2.33, 95% CI 1.02 to 5.28, P = 0.04, 3 studies, 513 participants, ITT analysis; Analysis 2.27)
- 5 mg/day donepezil at 24 weeks (43/662 donepezil, 55/673 placebo) (OR 0.78, 95% CI 0.52 to 1.18, P = 0.25, 4 studies, 1335 participants, ITT analysis; Analysis 2.27)
- 10 mg/day at 12 weeks (16/184 donepezil, 43/178 placebo) (OR 3.45, 95% CI 1.40 to 8.50, P = 0.007, 3 studies, 362 participants, ITT analysis; Analysis 2.27)
- 10 mg/day donepezil at 24 to 26 weeks (199/1431 donepezil, 121/1388 placebo) (OR 1.68, 95% CI 1.33 to 2.12, P < 0.00001, 11 studies, 2819 participants, ITT analysis; Analysis 2.27)
- 10 mg/day donepezil at 52 weeks (10/142 donepezil, 9/144 placebo) (OR 1.14, 95% CI 0.45 to 2.88, P = 0.79, 1 study, 286 participants, ITT analysis; Analysis 2.27)

Adverse events

The meta-analyses of numbers of participants with at least one adverse event showed a difference between the 5 mg/day group and placebo in favour of placebo, at 24 to 26 weeks but not at 12 weeks, and a similar result for the 10 mg/day donepezil.

- 5 mg/day donepezil at 12 weeks (106/157 donepezil, 106/153 placebo) (OR 1.08, 95% CI 0.70 to 1.67, P = 0.24, 3 studies, 513 participants, ITT analysis; Analysis 2.28)
- 5 mg/day donepezil at 24 to 26 weeks (346/508 donepezil, 317/510 placebo) (OR 1.40, 95% CI 1.06 to 1.86, P = 0.02, 3 studies, 1018 participants, ITT analysis; Analysis 2.28)
- 10 mg/day donepezil at 12 weeks (124/158 donepezil, 106/153 placebo) (OR 1.55, 95% CI 0.94 to 2.55, P = 0.09, 2 studies, 323 participants, ITT analysis; Analysis 2.28)
- 10 mg/day at 24 to 26 weeks (913/1274 donepezil, 793/1226 placebo) (OR 1.59, 95% CI 1.30 to 1.94, P < 0.000001, 10 studies, 2500 participants, ITT analysis; Analysis 2.28)
- 10 mg/day donepezil at 52 weeks (116/142 donepezil, 109/144 placebo) (OR 1.43, 95% CI 0.81 to 2.51, P = 0.22, 1 study, 286 participants, ITT analysis; Analysis 2.28)

The studies reported 53 different causes of adverse events. The causes of adverse events seen more frequently in the 10 mg/day dose group than in the 5 mg/day group or placebo group included nausea, vomiting and diarrhoea. These were mostly mild and transient, but occasionally moderately severe. There were differences, in favour of placebo, compared with donepezil, usually the 10 mg/day dose, for several causes of adverse events.

Anorexia

- 10 mg/day donepezil 24 to 26 weeks (67/962 donepezil, 21/969 placebo) (OR 3.01 95% CI 1.96 to 4.62, P < 0.00001, 6 studies, 1931 participants, ITT analysis; Analysis 2.35)

Diarrhoea

- 5 mg/day donepezil at 12 weeks (14/197 donepezil, 5/193 placebo) (OR 2.64 95% CI 1.05 to 6.63, P = 0.04, 2 studies, 390 participants, ITT analysis; Analysis 2.47)
- 10 mg/day donepezil at 12 weeks (21/158 donepezil, 4/153 placebo) (OR 4.22 95% CI 1.87 to 9.54, P = 0.0005, 1 study, 311 participants; Analysis 2.47)
- 5 mg/day donepezil at 24 to 26 weeks (53/662 donepezil, 30/672 placebo) (OR 1.85 95% CI 1.19 to 2.89, P = 0.007, 4 studies, 1334 participants, ITT analysis; Analysis 2.47)
- 10 mg/day donepezil at 24 to 26 weeks (166/1330 donepezil, 60/1292 placebo) (OR 2.69 95% CI 2.05 to 3.55, P < 0.00001, 9 studies, 2622 participants, ITT analysis; Analysis 2.47)

Dizziness

- 10 mg/day donepezil at 24 to 26 weeks (68/930 donepezil, 38/900 placebo) (OR 1.77 95% CI 1.19 to 2.63, P = 0.004, 6 studies, 1830 participants, ITT analysis; Analysis 2.48)

Fatigue

- 10 mg/day donepezil at 24 to 26 weeks (12/157 donepezil, 3/162 placebo) (OR 3.63, 95% CI 1.29 to 10.21, P = 0.01, 1 study, 319 participants, ITT analysis; Analysis 2.51)

Hallucinations

- 10 mg/day donepezil at 24 to 26 weeks (8/128 donepezil, 1/120 placebo) (OR 4.68, 95% CI 1.24 to 17.66, P = 0.02, 1 study, 248 participants, ITT analysis; Analysis 2.56)

Insomnia

- 10 mg/day donepezil at 12 weeks (28/158 donepezil, 8/153 placebo) (OR 3.38, 95% CI 1.69 to 6.76, P = 0.0006, 1 study, 311 participants, ITT analysis; Analysis 2.62)
- 10 mg/day donepezil at 24 to 26 weeks (39/546 donepezil, 15/497 placebo) (OR 2.40, 95% CI 1.38 to 4.15, P = 0.002, 3 studies, 1043 participants, ITT analysis; Analysis 2.62)

Muscle cramp

- 5 mg/day donepezil at 24 to 26 weeks (9/154 donepezil, 1/162 placebo) (OR 5.48, 95% CI 1.56 to 19.27, P = 0.008, 1 study, 316 participants, ITT analysis; Analysis 2.65)
- 10 mg/day donepezil at 24 to 26 weeks (12/157 donepezil, 1/162 placebo) (OR 6.00, 95% CI 1.98 to 18.18, P = 0.002, 1 study, 319 participants, ITT analysis; Analysis 2.65)

Nausea

- 10 mg/day donepezil at 12 weeks (34/158 donepezil, 12/153 placebo) (OR 2.95, 95% CI 1.58 to 5.51, P = 0.0007, 1 study, 311 participants, ITT analysis; Analysis 2.66)
- 10 mg/day donepezil at 24 to 26 weeks (144/1120 donepezil, 46/1064 placebo) (OR 3.06, 95% CI 2.26 to 4.14, P < 0.00001, 8 studies, 2184 participants, ITT analysis; Analysis 2.66)

Peripheral oedema

- 10 mg/day donepezil at 24 to 26 weeks (25/103 donepezil, 14/105 placebo) (OR 2.04, 95% CI 1.02 to 4.09, P = 0.04, 1 study, 208 participants, ITT analysis; Analysis 2.68)

Tremor

- 10 mg/day donepezil at 24 to 26 weeks (8/103 donepezil, 2/105 placebo) (OR 3.58, 95% CI 1.01 to 12.71, P = 0.05, 1 study, 208 participants, ITT analysis; Analysis 2.77)

Vertigo

- 10 mg/day donepezil at 52 weeks (11/142 donepezil, 3/144 placebo) (OR 3.36, 95% CI 1.15 to 9.82, P = 0.03, 1 study, 286 participants, ITT analysis; Analysis 2.80)

Vomiting

- 10 mg/day donepezil at 24 to 26 weeks (109/949 donepezil, 43/959 placebo) (OR 2.65, 95% CI 1.90 to 3.70, P < 0.00001, 6 studies, 1908 participants, Analysis 2.74)

Weight loss

- 10 mg/day donepezil at 24 to 26 weeks (34/404 donepezil, 19/407 placebo) (OR 1.90, 95% CI 1.08 to 3.35, P = 0.03, 3 studies, 811 participants, ITT analysis; Analysis 2.81)

There were significant differences between numbers suffering adverse events in the donepezil group compared with the placebo group in favour of donepezil at 12 weeks but not at 24 weeks for the following causes.

Increased cough

- 5 mg/day donepezil at 12 weeks (2/157 donepezil, 8/153 placebo) (OR 0.28 95% CI 0.08 to 1.00, P = 0.05, 1 study, 310 participants, ITT analysis; Analysis 2.63)

Peripheral oedema

- 5 mg/day donepezil at 12 weeks (1/157 donepezil, 8/153 placebo) (OR 0.20, 95% CI 0.05 to 0.74, P = 0.02, 1 study, 310 participants, ITT analysis; Analysis 2.68)

Urinary tract infection

- 5 mg/day donepezil at 12 weeks (10/157 donepezil, 20/153 placebo) (OR 0.47, 95% CI 0.22 to 0.99, P = 0.05, 1 study, 310 participants, ITT analysis; Analysis 2.79)
- 10 mg/day donepezil at 12 weeks (6/158 donepezil, 20/153 placebo) (OR 0.30, 95% CI 0.13 to 0.67, P = 0.003, 1 study, 311 participants, ITT analysis; Analysis 2.79)

The Winblad 2001 reported only causes of adverse events suffered by more than 5% of participants receiving donepezil.

Serious adverse events

The meta-analyses of numbers of participants with at least one serious adverse event showed no difference between the 5 mg/day group and placebo, and the 10 mg/day group and placebo, at 12, and 24 to 26 weeks, and a difference at 52 weeks in favour of placebo.

- 5 mg/day donepezil at 12 weeks (6/157 donepezil, 7/153 placebo) (OR 0.83, 95% CI 0.27 to 2.51, P = 0.74, 1 study 310 participants, Analysis 2.83)
- 5 mg/day donepezil at 24 weeks (35/526 donepezil, 49/541 placebo) (ITT analysis; OR 0.76, 95% CI 0.49 to 1.18, P = 0.22, 3 studies, 1067 participants, ITT analysis; Analysis 2.83)
- 10 mg/day donepezil at 12 weeks (6/158 donepezil, 7/153 placebo) (OR 0.82, 95% CI 0.27 to 2.50, P = 0.73, 1 study, 311 participants, ITT analysis; Analysis 2.83)
- 10 mg/day donepezil at 24 to 26 weeks (148/1301 donepezil, 161/1298 placebo) (OR 0.90, 95% CI 0.71 to 1.14, P = 0.38, 9 studies, 2599 participants, ITT analysis; Analysis 2.83)
- 10 mg/day donepezil at 52 weeks (35/142 donepezil, 20/144 placebo) (OR 1.99, 95% CI 1.11 to 3.59, P = 0.02, 1 study, 286 participants, ITT analysis; Analysis 2.83)

Deaths

The meta-analyses of numbers of deaths showed no difference between the 5 mg/day group and placebo, and the 10 mg/day group and placebo, at 12, 24 to 26 weeks and at 52 weeks.

- 5 mg/day donepezil at 12 weeks (1/260 donepezil, 1/253 placebo) (OR 0.96, 95% CI 0.06 to 15.29, P = 0.97, 3 studies, 513 participants, ITT analysis; Analysis 2.82)
- 5 mg/day donepezil at 24 weeks (4/662 donepezil, 4/672 placebo) (OR 1.02, 95% CI 0.25 to 4.10, P = 0.98, 4 studies, 1334 participants, ITT analysis; Analysis 2.82)
- 10 mg/day donepezil at 12 weeks (0/158 donepezil, 1/153 placebo) (OR 0.13, 95% CI 0.00 to 6.60, P = 0.31, 1 study, 311 participants, ITT analysis; Analysis 2.82)
- 10 mg/day donepezil at 24 to 26 weeks (32/1445 donepezil, 41/1402 placebo) (OR 0.74, 95% CI 0.46 to 1.19, P = 0.21, 12 studies, 2847 participants, ITT analysis; Analysis 2.82)
- 10 mg/day donepezil at 52 weeks (4/142 donepezil, 3/144 placebo) (OR 1.36, 95% CI 0.30 to 6.07, P = 0.69, 1 study, 286 participants, ITT analysis; Analysis 2.82)

Quality of life

There was no evidence of any benefit associated with donepezil in the patient-rated Quality-of-Life scale at doses of either 5 mg/day or 10 mg/day compared with placebo at 12 or 24 weeks.

- 5 mg/day donepezil at 12 weeks (MD 1.18, 95% CI -3.04 to 5.40, P = 0.58, 4 studies, 1127 participants, ITT analysis; Analysis 2.20)
- 10 mg/day donepezil at 12 weeks (MD 1.16, 95% CI -3.20 to 5.52, P = 0.60, 4 studies, 1031 participants, ITT analysis; Analysis 2.20)
- 5 mg/day donepezil at 24 weeks (MD 2.26, 95% CI -3.64 to 8.16, P = 0.45, 2 studies, 681 participants, ITT analysis; Analysis 2.20)
- 10 mg/day donepezil at 24 weeks (MD -1.17, 95% CI -7.26 to 4.91, P = 0.71, 2 studies, 645 participants, ITT analysis; Analysis 2.20).

Carer stress

Lebert 1999 assessed the stress on carers but reported the results without any measure of precision.

Comparison of donepezil (10 mg/day) with placebo (patient and carer health resource utilisation)

Feldman 2001 and Winblad 2001 assessed this outcome. We did not pool the studies as we did not consider the outcomes to be comparable across studies. Many items were assessed and reported separately, and total costs were reported. There were no significant differences between donepezil and placebo apart from total carer costs (counselling, visits to physician and medication) in favour of placebo (MD 31.00, 95% CI 7.22 to 54.78, P = 0.01, one study, 289 participants; Analysis 3.3).

Comparison of donepezil 5 mg/day with donepezil 10 mg/day

The phase III studies were designed not only to compare donepezil with placebo, but also to compare two doses, 5 mg/day and 10 mg/day. We pooled results from the three 26-week studies, Homma 2008, Rogers 1998b and Burns 1999.

Cognitive function

There was a significant difference in favour of the 10 mg group for ADAS-Cog (MD -1.05, 95% CI -1.80 to -0.30, P = 0.006, 2 studies, 818 participants, ITT analysis; Analysis 7.1), but no difference between the groups for MMSE (MD 0.15, 95% CI -0.55 to 0.85, P = 0.67, 1 study, 303 participants, ITT analysis; Analysis 7.2), or SIB (MD 2.20, 95% CI -1.00 to 5.40, P = 0.18, 1 study, 188 participants, ITT analysis; Analysis 7.3).

Quality of life

There was a difference in favour of the 5 mg/day group for quality of life (MD -8.33, 95% CI -16.23 to -0.43, P = 0.04, 1 study, 302 participants; Analysis 7.8).

Global assessment

There was no difference between the 10 mg/day and 5 mg/day groups at 24 to 26 weeks for the global assessment using CIBIC-plus (OR 1.26, 95% CI 0.94 to 1.67, P = 0.12, 3 studies, 981 participants, ITT analysis; Analysis 7.5), or CDR-SB (MD -0.08, 95% CI -0.29 to 0.14, P = 0.48, 2 studies, 824 participants, ITT analysis; Analysis 7.6).

Behavioural symptoms

There was no difference between the 10 mg/day and 5 mg/day groups at 24 to 26 weeks for the BEHAVE-AD (MD 0.40, 95% CI -1.27 to 2.07, 1 study, 198 participants, ITT analysis; Analysis 7.7).

Withdrawals before the end of treatment

The meta-analyses of withdrawals before the end of treatment at 24 to 26 weeks, using the OR, showed differences in withdrawals in favour of the 5 mg/day group (143/526 10 mg/day, 96/526 5 mg/day) (OR 1.67, 95% CI 1.24 to 2.23, P = 0.0006, 3 studies, 1052 participants, ITT analysis; Analysis 7.9).

Withdrawals before the end of treatment due to adverse events

The meta-analyses of withdrawals before the end of treatment at 24 to 26 weeks, due to an adverse event, using the OR, show that

there was a difference in favour of the 5 mg/day group (89/526 10 mg/day, 41/526 5 mg/day) (OR 2.41 95% CI 1.63 to 3.57, P < 0.0001, 3 studies, 1052 participants, ITT analysis; Analysis 7.10).

Adverse events

The meta-analyses of the total number of participants who suffered at least one adverse event showed a difference in favour of the 5 mg/day group (314/369 10 mg/day, 292/372 5 mg/day) (OR 1.56, 95% CI 1.07 to 2.28, P = 0.02, 2 studies,741, ITT analysis; Analysis 7.11).

There were significant differences, in favour of 5 mg/day, compared with 10 mg/day, for several causes of adverse events. The adverse events seen more frequently in the 10 mg/day group than in the 5 mg/day group were anorexia, nausea, diarrhoea, rhinitis and vomiting.

- Anorexia: (39/526 10 mg/day, 15/526 5 mg/day) (OR 2.72, 95% CI 1.48 to 5.00, P = 0.001, 3 studies, 1052 participants, ITT analysis; Analysis 7.12)
- Diarrhoea: (80/526 10 mg/day, 48/526 5 mg/day) (OR 1.78 ,95% CI 1.22 to 2.61, P = 0.003, 3 studies, 1052 participants, ITT analysis; Analysis 7.14)
- Nausea: (92/430 10 mg/day, 26/425 5 mg/day) (OR 4.22, 95% CI 2.67 to 6.70, P < 0.00001, 2 studies, 855 participants, ITT analysis; Analysis 7.20)
- Rhinitis: (9/157 10 mg/day, 1/154 5 mg/day) (OR 9.30, 95% CI 1.16 to 74.35, P = 0.04, 1 study, 311 participants, ITT analysis; Analysis 7.21)
- Vomiting: (73/526 10 mg/day, 24/526 5 mg/day) (OR 3.40, 95% CI 2.10 to 5.48, P < 0.00001, 3 studies, 1052 participants, ITT analysis; Analysis 7.22)

Comparison of donepezil (15-20 mg/day) with donepezil (10 mg/day)

Schindler 2004 reported the number of adverse events in 26 weeks of treatment when participants already taking 10 mg/day of donepezil were randomised to either placebo or a further 5 mg/day or 10 mg/day of donepezil. There was no difference between treatment and placebo (that is, between 15-20 mg/day and 10 mg/day) (6/16 15-20 mg/day, 4/15 10 mg/day) (OR 1.65, 95% CI 0.36 to 7.60, P = 0.52, 1 study, 31 participants, ITT analysis; Analysis 5.1). Schindler 2004 did not assess cognitive function.

Comparison of donepezil (10 mg/day) with placebo at 12 weeks for participants with severe agitation

One study included participants with severe agitation, Howard 2007. There was no difference between donepezil (13/128), and placebo (19/131) for withdrawals before end of treatment (OR 0.67, 95% CI 0.31 to 1.41, P = 0.29, 1 study, 259 participants, Analysis 6.4), CMAI (MD 0.18, 95% CI -4.23 to 4.59, P = 0.94 , 1 study 221 participants, Analysis 6.1), NPI (MD 0.10, 95% CI -3.78 to 3.98, P = 0.96, 1 study, 201 participants, Analysis 6.2), and NPI-carer distress (MD -0.45, 95% CI -2.06 to 1.16, P = 0.58, 1 study, 200 participants, Analysis 6.3). The SIB and MMSE were also outcomes but less than half of the participants were able to complete these assessments.

Comparison of donepezil (23 mg/day) with donepezil (10 mg/day)

Cognitive Function

There was no significant difference between the 23 mg group and the 10 mg group for SIB (MD 1.05, 95% CI -0.15 to 2.25, P = 0.09, 2 studies, 1704 participants, ITT analysis; Analysis 4.1), and there was no difference between the groups for the MMSE (MD 0.20, 95% CI -0.33 to 0.73, P = 0.46, 1 study, 1370 participants, ITT analysis; Analysis 4.2).

Activities of daily living

There was no difference between the groups for the ADCS-ADL-sev (MD 0.0, 95% CI -1.18 to 1.18, 1 study, 1369 participants, ITT analysis; Analysis 4.3).

Global assessment

There was no difference between the groups for the CIBIC-plus (OR 0.99, 95% CI 0.78 to 1.26, P = 0.93, 2 studies, 1704 participants, ITT analysis; Analysis 4.4).

Withdrawals before the end of treatment

The meta-analysis of withdrawals before the end of treatment at 24 to 26 weeks, using the OR, showed a significant difference in withdrawals in favour of the 10 mg/day group (112/652), compared with the 23 mg/day group (348/1166), (OR 2.02, 95% CI 1.59 to 2.57, P < 0.00001, 2 studies, 1818 participants, ITT analysis; Analysis 4.5).

Withdrawals before the end of treatment due to adverse events

The meta-analysis of withdrawals before the end of treatment due to adverse events at 24 to 26 weeks, using the OR, showed a significant difference in withdrawals in favour of the 10 mg/day group (54/652) compared with the 23 mg group (215/1166), (OR 2.51, 95% CI 1.83 to 3.45, P < 0.00001, 2 studies, 1818 participants, ITT analysis; Analysis 4.6).

Adverse events

The meta-analyses of the total number of participants who suffered at least one adverse event showed a significant difference in favour of the 10 mg/day group (398/637), compared with the 23 mg/day group (844/1148) at 24 to 26 weeks, (OR 1.65, 95% CI 1.34 to 2.03, P < 0.0001, 1 study, 1785 participants, ITT analysis; Analysis 4.7).

There was no difference between the groups for the numbers of participants who suffered a serious adverse event at 24 to 26 weeks (103/1148 23 mg/day, 59/637 10 mg/day) (OR 0.99, 95% CI 0.71 to 1.38, P = 0.94. 2 studies, 1785 participants, ITT analysis; Analysis 4.8).

There were significant differences, in favour of 10 mg/day, compared with 23 mg/day, for several causes of adverse events. The adverse events seen more frequently in the 23 mg/day dose group than in the 105 mg/day group were asthenia, anorexia, contusion, nausea, vomiting and diarrhoea, fatigue and bradycardia.

- Anorexia: (51/963 23 mg/day, 8/471 10 mg/day) (OR 3.24, 95% CI 1.52 to 6.88, P = 0.002, 1 study, 1434 participants, ITT analysis; Analysis 4.11)
- Asthenia: (20/963 23 mg/day, 3/471 10 mg/day) (OR 3.31, 95% CI 0.98 to 11.19, P = 0.05, 1 study, 1434 participants, ITT analysis; Analysis 4.9)
- Bradycardia: (27/963 23 mg/day, 3/471 10 mg/day) (OR 4.50, 95% CI 1.36 to 14.91, P = 0.01, 1 study, 1434 participants, ITT analysis; Analysis 4.22)
- Contusion: (34/1148 23 mg/day, 5/63710 mg/day) (OR 4.9997, 95% CI 1.88 to 13.26, P = 0.001, 2 studies, 1785 participants, ITT analysis; Analysis 4.10)
- Diarrhoea: (94/1148 23 mg/day, 30/637 10 mg/day) (OR 1.76, 95% CI 1.15 to 2.68, P = 0.009, 2 studies, 1785 participants, ITT analysis; Analysis 4.12)
- Fatigue: (23/963 23 mg/day, 4/471 10 mg/day) (OR 2.86, 95% CI 0.98 to 8.31, P = 0.05, 1 study, 1434 participants, ITT analysis; Analysis 4.14)
- Nausea: (123/1148 23 mg/day, 21/637 10 mg/day) (OR 3.36, 95% CI 2.09 to 5.42, P < 0.00001, 2 studies, 1785 participants, ITT analysis; Analysis 4.17)
- Vomiting: (105/1148 23 mg/day, 16/637 10 mg/day) (OR 3.88, 95% CI 2.27 to 6.65, P < 0.00001, 2 studies, 1785 participants, ITT analysis; Analysis 4.18)

Deaths

There was no difference between the groups for the numbers of participants who died before end of treatment at 24 to 26 weeks (8/1148 23 mg/day, 6/637 10 mg/day) (OR 0.69, 95% CI 0.24 to 1.95, P = 0.48, 2 studies, 1785 participants, ITT analysis; Analysis 4.27).

Comparison of donepezil (5 mg/day and 10 mg/day) with placebo in participants with severe dementia

Cognitive function

The MMSE, using MDs, showed a benefit on cognitive function in favour of the higher-dose donepezil compared with placebo at 24 weeks.

- 10 mg/day donepezil at 24 weeks (MD 0.97, 95% CI 0.56 to 1.38, P = <0.00001, 4 studies, 1102 participants, ITT analysis; Analysis 8.1)

The meta-analyses, using MDs, revealed a benefit on cognitive function as measured by SIB test scores for the lower-dose and higher-dose donepezil compared with placebo at 24 weeks.

- 5 mg/day donepezil at 24 weeks (MD 6.70, 95% CI 3.66 to 9.74, P < 0.0001, 1 study, 198 participants, ITT analysis; Analysis 8.2)
- 10 mg/day donepezil at 24 weeks (MD 5.92, 95% CI 4.53 to 7.31, P < 0.00001, 5 studies, 1348 participants, ITT analysis; Analysis 8.2).

Activities of daily living

Winblad 2006, Homma 2008 and Black 2007 used the ADCS-ADL-severe scale. There was evidence of benefit of 10 mg/day donepezil at 24 weeks (MD 1.03, 95% CI 0.21 to 1.85, P = 0.01, 3 studies, 733 participants, ITT analysis; Analysis 8.4), but not for 5 mg/day at 24 weeks (MD 1.00, 95% CI -0.54 to 2.54, P = 0.20, 1 study, 198 participants, ITT analysis; Analysis 8.4).

Dependency

Feldman 2001 assessed the time spent each day by the carer assisting with the activities of daily living but there was no evidence of a treatment effect. 10 mg/day donepezil at 24 weeks (MD -52.4, 95% CI -118.78 to 13.98, P = 0.12, 1 study, 221 participants, ITT analysis; Analysis 8.7).

Global assessment

We dichotomised the seven-point CIBIC-Plus scale, measuring global clinical state, counting those showing no change or decline, against those showing improvement, and analysed the results using the OR. There were benefits associated with 10 mg/day donepezil compared with placebo at 24 weeks as shown by the ITT analyses, but not with 5 mg/day.

- 5 mg/day donepezil at 24 weeks (31/96 donepezil, 24/102 placebo) (OR 1.54, 95% CI 0.83 to 2.87, P = 0.17, 1 study, 198 participants, ITT analysis; Analysis 8.3)
- 10 mg/day donepezil at 24 weeks (151/379 donepezil, 103/376 placebo) (OR 1.78, 95% CI 1.31 to 2.43, P = 0.0002, 3 studies, 755 participants, ITT analysis; Analysis 8.3)

Behavioural symptoms

Feldman 2001, Winblad 2006, and Black 2007 assessed behavioural disturbance (NPI-TOTAL), and there was evidence of benefit of donepezil 10 mg/day at 24 weeks.

- 10 mg/day donepezil at 24 weeks (MD -2.18, 95% CI -4.11 to -0.25, P = 0.03, 3 studies, 827 participants, ITT analysis; Analysis 8.6)

Homma 2008 assessed BEHAVE-AD and there was no evidence of benefit of donepezil.

- 5 mg/day donepezil at 24 weeks (MD 0.00, 95% CI -1.67 to 1.67, P = 1.00, 1 study, 198 participants, ITT analysis; Analysis 8.5)
- 10 mg/day donepezil at 24 weeks (MD 0.40, 95% C I -1.28 to 2.08, P = 0.64, 1 study, 194 participants, ITT analysis; Analysis 8.5)

Withdrawals before the end of treatment

The meta-analyses of withdrawals before the end of treatment, using the OR, showed significant differences in withdrawals between the 10 mg/day group and the placebo group in favour of placebo at 24 weeks, but not for the 5 mg/day group.

- 5 mg/day donepezil at 24 weeks (13/101 donepezil, 19/105 placebo) (OR 0.67, 95% CI 0.32 to 1.43, P = 0.30, 1 study, 206 participants, ITT analysis; Analysis 8.8).
- 10 mg/day donepezil at 24 weeks (164/701 donepezil, 130/695 placebo) (OR 1.32, 95% CI 1.02 to 1.71, P = 0.04, 5 studies, 1396 participants, ITT analysis; Analysis 8.8).

Withdrawals before the end of treatment due to adverse events

The meta-analyses of withdrawals before the end of treatment due to adverse events, using the OR, showed significant differences in withdrawals between the 10 mg/day group at 24 weeks in favour of placebo, but not for the 5 mg/day group.

- 5 mg/day donepezil at 24 weeks (8/101 donepezil, 11/105 placebo) (OR 0.74, 95% CI 0.29 to 1.89, P = 0.53, 1 study, 206 participants, ITT analysis; Analysis 8.9).
- 10 mg/day donepezil at 24 weeks (93/701 donepezil, 55/695 placebo) (OR 1.72, 95% CI 1.23 to 2.42, P = 0.002, 5 studies, 1396 participants, ITT analysis; Analysis 8.9).

Adverse events

The meta-analyses of numbers of participants with at least one adverse event showed a significant difference between the 10 mg/day group and placebo in favour of placebo, at 24 weeks but not for the 5 mg/day donepezil.

- 5 mg/day donepezil at 24 weeks(79/101 donepezil, 77/105 placebo) (OR 1.30, 95% CI 0.69 to 2.46, P = 0.41, 1 study, 206 participants, ITT analysis; Analysis 8.10).
- 10 mg/day at 24 weeks (487/701 donepezil, 328/695 placebo) (OR 1.59, 95% CI 1.23 to 2.05, P = 0.0003, 5 studies, 1396 participants, ITT analysis; Analysis 8.10)

The included studies reported 32 different causes of adverse events. The causes of adverse events seen more frequently in the 10 mg/day dose group than in the 5 mg/day group or placebo group included nausea, vomiting and diarrhoea. These were mostly mild and transient, but occasionally moderately severe. There were significant differences, in favour of placebo, compared with donepezil, usually the 10 mg/day dose, for several causes of adverse events.

- Anexoria: 10 mg/day donepezil 24 weeks (26/429 donepezil, 141/428 placebo) (OR 2.32 95% CI 1.20 to 4.48, P = 0.01, 3 studies, 857 participants, ITT analysis; Analysis 8.14)
- Arthralgia: 10 mg/day donepezil 24 weeks (10/144 donepezil, 2/146 placebo) (OR 4.06 95% CI 1.28 to 12.86, P = 0.02, 1 study, 290 participants, ITT analysis; Analysis 8.16)
- Diarrhoea: 10 mg/day donepezil at 24 weeks (60/701 donepezil, 20/694placebo) (OR 2.57 95% CI 1.65 to 4.01, P < 0.0001, 5 studies, 1395 participants, ITT analysis; Analysis 8.25)
- Hallucinations: 10 mg/day donepezil at 24 weeks (8/128 donepezil, 1/120 placebo) (OR 4.68, 95% CI 1.24 to 17.66, P = 0.02, 1 study, 248 participants, ITT analysis; Analysis 8.30)
- Headache: 10 mg/day donepezil at 24 weeks (17/144 donepezil, 6/146 placebo) (OR 2.86, 95% CI 1.22 to 6.69, P = 0.02, 1 study, 290 participants, ITT analysis; Analysis 8.37)
- Insomnia: 10 mg/day donepezil at 24 weeks (12/176 donepezil, 4/167 placebo) (OR 2.70, 95% CI 0.99 to 7.35, P = 0.05, 1 study, 343 participants, ITT analysis; Analysis 8.33)
- Nausea: 10 mg/day donepezil at 24 weeks (31/424 donepezil, 14/404 placebo) (OR 2.11, 95% CI 1.16 to 3.85, P = 0.01, 3 studies, 828 participants, ITT analysis; Analysis 8.35)
- Restlessness: 5 mg/day donepezil at 24 weeks (6/101 donepezil, 1/105 placebo) (OR 4.54, 95% CI 1.01 to 20.41, P = 0.05, 1 study, 206 participants, ITT analysis; Analysis 8.36)
- Vomiting: 10 mg/day donepezil at 24 weeks (35/416 donepezil, 15/418 placebo) (OR 2.42, 95% CI 1.37 to 4.31, P = 0.002, 3 studies, 834 participants, ITT analysis; Analysis 8.39)

Serious adverse events

The meta-analyses of numbers of participants with at least one serious adverse event showed no difference between the 5 mg/day group and placebo, and the 10 mg/day group and placebo, at 24 weeks.

- 5 mg/day donepezil at 24 weeks(12/101 donepezil, 15/105 placebo) (OR 0.81, 95% CI 0.36 to 1.82, P = 0.61, 1 study, 206 participants, ITT analysis; Analysis 8.44).
- 10 mg/day at 24 weeks (90/701 donepezil, 107/695 placebo) (OR 0.80, 95% CI 0.59 to 1.08, P = 0.14, 5 studies, 1396 participants, ITT analysis; Analysis 8.44)

Deaths

The meta-analyses of numbers of deaths before end of treatment at 24 weeks showed no difference between the 5 mg/day group and placebo, and the 10 mg/day group and placebo, at 24 weeks.

- 5 mg/day donepezil at 24 weeks (2/101 donepezil, 1/105 placebo) (OR 2.04, 95% CI 0.21 to 19.83, P = 0.54, 1 study, 206 participants, ITT analysis; Analysis 8.43).
- 10 mg/day at 24 weeks (24/701 donepezil, 31/695 placebo) (OR 0.71, 95% CI 0.41 to 1.25, P = 0.24, 5 studies, 1396 participants, ITT analysis; Analysis 8.43

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Donepezil 23 mg/day compared with donepezil 10 mg/day for dementia due to Alzheimer's disease

Patient or population: people with Alzheimer's disease
Settings: worldwide
Intervention: donepezil 23 mg/day for 24 weeks
Comparison: donepezil 10 mg/day for 24 weeks

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Donepezil 10 mg/day	Donepezil 23 mg/day				
Cognitive function (change from baseline at 24 weeks using SIB)[1]		The mean score in the donepezil 23 mg/day group was 1.05 higher (0.15 lower to 2.25 higher) than in the donepezil 10 mg/day group		1704 (2 studies)	⊕⊕⊕◯ **moderate**[2]	SIB has a maximum score of 100 points, a lower score indicates greater impairment.There was no significant difference between the 2 groups
Cognitive function (change from baseline at 24 weeks using MMSE)[1]		The mean score in the donepezil 23 mg/day group was 0.20 higher (0.33 lower to 0.73 higher) than in the donepezil 10 mg/day group		1370 (1 study)	⊕⊕⊕◯ **moderate**[2]	MMSE has a maximum score of 30 points, a lower score indicates greater impairment. There was no significant difference between the 2 groups
Activities of daily living (change from baseline at 24 weeks using the ADCS-ADL-sev)[1]		The mean score in the donepezil 23 mg/day group was 0 higher (1.18 lower to 1.18 higher) than in the donepezil 10 mg/day group		1396 (1 study)	⊕⊕⊕◯ **moderate**[2]	There was no significant difference between the 2 groups

Clinician-rated global impression test (improved compared with baseline assessed using CIBIC-plus at 24 weeks)[1]	**212 per 1000**	**210 per 1000** (173 to 253)	**OR 0.99** (0.78 to 1.26)	1704 (2 studies)	⊕⊕⊕◯ **moderate**[2]	There was no significant difference between the 2 groups
Acceptability of treatment (as measured by withdrawals from trial before end of treatment at 24 weeks)[1]	**172 per 1000**	**296 per 1000** (248 to 348)	**OR 2.02** (1.59 to 2.57)	1818 (2 studies)	⊕⊕⊕◯ **moderate**[2]	
Incidence of adverse events (at least one adverse event by 24 weeks)[1]	**624 per 1000**	**732 per 1000** (690 to 771)	**OR 1.65** (1.34 to 2.03)	1785 (2 studies)	⊕⊕⊕◯ **moderate**[2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ADCS-ADL-sev: Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (severe version); **CI:** confidence interval; **CIBIC**: Clinician's Interview-Based Impression of Change; **MMSE**: Mini-Mental State Examination; **OR:** odds ratio; **SIB**: Severe Impairment Battery

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]All statistics are based on the analyses of the intention to treat last observation carried forward (ITT-LOCF) population. Although using the ITT population in the analyses for studies in degenerative conditions can be criticised as substitution of the LOCF when a patients is lost before end point may enhance the outcome, in this review the results of the analyses of the population who completed the study were similar to the ITT results and did not alter our conclusions.
[2]Downgraded one level due to the risk of bias due to lack of information on the blinding of outcome assessment.

Donepezil 10 mg/day compared with donepezil 5 mg/day for dementia due to Alzheimer's disease

Patient or population: people with Alzheimer's disease
Settings: worldwide
Intervention: donepezil 10 mg/day
Comparison: *donepezil 5 mg/day

Outcomes	Assumed risk	Corresponding risk	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Donepezil 5 mg/day	Donepezil 10 mg/day				
Cognitive function (change from baseline at 24 weeks using ADAS-Cog)[1]		The mean score in the donepezil 10 mg/day group was 1.05 lower (1.80 lower to 0.30 lower) than in the donepezil 5 mg/day group		818 (2 studies)	⊕⊕⊕◯ **moderate**[2]	ADAS-Cog score has a maximum of 70 points, the lower score in the donepezil 10 mg/day group indicates greater improvement
Cognitive function (change from baseline at 24 weeks using MMSE)[1]		The mean score in the donepezil 10 mg/day group was 0.15 higher (-0.55 to 0.85 higher) than in the donepezil 5 mg/day group		303 (1 study)	⊕⊕⊕◯ **moderate**[2]	MMSE has a maximum score of 30 points, a lower score indicates greater impairment
Clinician-rated global impression test (improved compared with baseline assessed using CIBIC-plus at 24 weeks)[1]	**246 per 1000**	**291 per 1000** (235 to 353)	**OR 1.26** (0.94 to 1.67)	981 (3 studies)	⊕⊕⊕◯ **moderate**[2]	
Acceptability of treatment (as measured by withdrawals from trial before end of treatment at	**183 per 1000**	**272 per 1000** (217 to 333)	**OR 1.67** (1.24 to 2.23)	1052 (3 studies)	⊕⊕⊕◯ **moderate**[2]	

24 weeks)[1]					
Incidence of adverse events (at least one adverse event by 24 weeks)[1]	**785per 1000**	**851 per 1000** (796 to 893)	**OR 1.56** (1.07 to 2.28)	741 (2 studies)	⊕⊕⊕◯ **moderate**[2]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive; **CI:** confidence interval; **CIBIC**: Clinician's Interview-Based Impression of Change; **MMSE**: Mini-Mental State Examination; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]All statistics are based on the analyses of the intention to treat last observation carried forward (ITT-LOCF) population. Although using the ITT population in the analyses for studies in degenerative conditions can be criticised as substitution of the LOCF when a patients is lost before end point may enhance the outcome, in this review the results of the analyses of the population who completed the study were similar to the ITT results and did not alter our conclusions.
[2]Downgraded one level due to the risk of bias due to lack of information on the blinding of outcome assessment and of blinding of participants.

Donepezil 10 mg/day compared with placebo for people with severe dementia due to Alzheimer's disease

Patient or population: people with severe Alzheimer's disease
Settings: worldwide
Intervention: donepezil 10 mg/day for 24 weeks
Comparison: placebo for 24 weeks

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Donepezil 10 mg/day				
Cognitive function (change from baseline at 26 weeks using MMSE)		The mean score in the donepezil group was 0.97 higher (0.56 higher to 1.38 higher) than in the placebo group		1102 (4 studies)	⊕⊕⊕◯ **moderate**	MMSE has a maximum score of 30 points, a lower score indicates greater impairment. Treatment effect was in favour of donepezil
Cognitive function (change from baseline at 24 weeks using SIB) [1]		The mean score in the donepezil 10 mg/day group was 5.92 higher (4.53 higher to 7.31 higher) than in the placebo group		1348 (5 studies)	⊕⊕⊕◯ **moderate**	SIB has a maximum score of 100 points, a lower score indicates greater impairment
Clinician-rated global impression tests (improved compared with baseline, measured using CIBIC-Plus at 24 weeks)[1]	**274 per 1000**	**402 per 1000** (331 to 478)	**OR 1.78 (1.31 to 2.43)**	755 (3 studies)	⊕⊕⊕◯ **moderate**	

Activities of daily living (change from baseline at 24 weeks using the ADCS-ADL-sev)[1]		The mean score in the donepezil 10 mg/day group was 1.03 higher 0.21 higher to 1. 85 higher) than in the placebo group		733 (3 studies)	⊕⊕⊕◯ **moderate**	The higher score indicates greater improvement.
Acceptability of treatment (as measured by withdrawals from trial before end of treatment at 24 weeks)[1]	**187 per 1000**	**233 per 1000** (190 to 282)	**OR 1.32** (1.02 to 1.71)	1396 (5 studies)	⊕⊕⊕◯ **moderate**	Withdrawals significantly more frequent in the donepezil group compared with placebo group
Incidence of adverse events (at least one adverse event by 24 weeks)[1]	**616 per 1000**	**718 per 1000** (664 to 767)	**OR 1.59** (1.23 to 2.05)	1396 (5 studies)	⊕⊕⊕◯ **moderate**	Adverse events significantly more frequent in the donepezil group compared with placebo group

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ADCS-ADL-sev: Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (severe version); **CI:** confidence interval; **CIBIC**: Clinician's Interview-Based Impression of Change; **MMSE**: Mini-Mental State Examination; **OR:** odds ratio; **SIB**: Severe Impairment Battery

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
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Low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]All statistics are based on the analyses of the intention to treat last observation carried forward (ITT-LOCF) population. Although using the ITT population in the analyses for studies in degenerative conditions can be criticised as substitution of the LOCF when a patients is lost before end point may enhance the outcome, in this review the results of the analyses of the population who completed the study were similar to the ITT results and did not alter our conclusions.
[2] Downgraded one level due to the risk of bias due to lack of information on allocation concealment and on the blinding of outcome assessment.

DISCUSSION

Summary of main results

The main findings of the review were as follows.

- The currently recommended dose of donepezil (10 mg/day) has benefits compared with placebo at 26 weeks for cognitive function, activities of daily living and the clinician-rated global impression scales. We found no difference for behavioural symptoms or quality of life. Participants on donepezil were more likely to experience adverse events (OR of 1.6) or to withdraw from the trial before the end.
- Participants on a lower dose of 5 mg/day were less likely to experience adverse events or to withdraw from the trial compared with participants on 10 mg/day. The higher dose showed some benefit for cognitive function, but not for activities of daily living and clinician-related global impression compared with the lower dose.
- A higher dose of 23 mg/day from a slow-release formulation had no benefits for cognitive function, activities of daily living and clinician-rated global impression scales compared with the 10 mg/day dose, but participants on the higher dose were more likely to experience adverse events or to withdraw from the trial compared with participants on the lower dose.
- Four studies only included participants with severe or moderately severe dementia. The results from these four studies reported similar results to the studies that included only participants with mild to moderate dementia.

Outcomes

The included studies used three cognitive tests. The MMSE and the ADAS-Cog assess similar domains and the results of the meta-analyses were similar. The results from five studies showed that 10 mg daily of donepezil improved cognitive function of participants with mild to moderate probable Alzheimer's disease treated over a period of 24 to 26 weeks by 1.1 points on the MMSE (range 0 to 30) and by 2.7 points on the ADAS-Cog (range 0 to 70), when compared with placebo. The results from five studies showed that 10 mg/day of donepezil improved cognitive function of participants with moderately severe to severe probable Alzheimer's disease treated over a period of 24 weeks by 5.9 points on the SIB (range 0 to 100) when compared with placebo.

Three studies assessed the effect of 10 mg/day donepezil on activities of daily living using the ADCS-ADL-sev scale (range 0 to 54). Donepezil showed a benefit of 1.0 points compared with placebo. When we dichotomised the results of the clinician-rated global impression measures to compare the number of participants who showed no change or whose condition had deteriorated with the number who had improved, the 10 mg/day donepezil group was significantly better than the placebo group at 24 to 26 weeks.

There was very little evidence on the effect of donepezil on behavioural problems, which only five studies assessed. In none of the studies did the participants suffer from more than mild problems at baseline. We found no evidence that donepezil affects patient-rated quality of life measured on the scale chosen for these studies. Lebert 1999 assessed stress on carers but reported the results without any measure of precision and so we have not included them in this review.

Adverse effects

Donepezil appears to have a low incidence of serious side effects. The earlier studies (Rogers 1998a; Rogers 1998b; Burns 1999) used a short titration period of one week on 5 mg/day before proceeding to the 10 mg/day dose but later studies used a four-week titration period, as recommended by the pharmaceutical company in the prescribing information. There were significantly more total dropouts and dropouts due to adverse events from the 10 mg/day group than from the placebo or 5 mg/day groups, and therefore side effects remain a clinical issue.

Overall completeness and applicability of evidence

We were able to include evidence from both published and unpublished studies in this systematic review. Most of the studies were sponsored by the pharmaceutical industry. The participants had mainly mild to moderate dementia due to Alzheimer's disease. In six studies participants were included with a MMSE less than 12. These participants were excluded from most of the other included studies. When these results are added to the meta-analyses the results appear very similar to those of participants with mild to moderate dementia. Although the MMSE measurements are in a different part of the MMSE scale, the treatment effect is very similar to the other studies. In the studies of people with severe dementia, the SIB was also used to assess cognitive function, a scale designed for use with people with severe dementia. There is no evidence of a different rate of withdrawals or rates of adverse events from the studies of participants with severe dementia, compared with the studies of participants with mild to moderate dementia. The death rate is higher for participants with severe dementia compared to the participants with mild to moderate dementia, but this reflects the greater age of the people in the severe stage of dementia compared with the milder stages. There is no difference between the death rates for the treatment and placebo groups.

The main limitation in the completeness and applicability of the evidence was the lack of long-term data beyond 26 weeks. One study reported data at 52 weeks. There were relatively few data on outcomes important to patients and carers, such as quality of life.

Quality of the evidence

The quality of the evidence at 26 weeks is moderate for most outcomes.

In terms of measuring outcomes and statistical analysis, the donepezil studies have essentially followed the relevant FDA guidance. The results reported are on an ITT basis, based on the participants' last assessments during the double-blind phase (so-called Last Observation Carried Forward LOCF analysis). As participants who did not complete the trial would, on average, show a further decline by the end of the double-blind phase, this substitution of the LOCF is likely to enhance the final outcome. This effect is of significance when large numbers drop out and when there is differential dropout across the treatment groups. In these studies the latter effect applies to the 10 mg/day donepezil group, where there is a slightly greater dropout rate compared with placebo (27% compared with 21%), which is probably related to treatment. However, we have reported the results from the analysis of the ITT and completers' data, and found that the loss of participants from the studies did not alter our conclusions.

Potential biases in the review process

One review extracted the data and the same review author checked them. This was considered adequate when the previous versions of the review were written as the reviewer is a professional statistician. There have been no errors in data extraction reported.

Agreements and disagreements with other studies or reviews

The most recent systematic reviews of cholinesterase inhibitors have included all three cholinesterase inhibitors, donepezil, rivastigmine and galantamine, in the review. Tan 2014 included all three cholinesterase inhibitors and reported results for each separately. Tan 2014 included 10 studies comparing donepezil 10 mg/day with placebo and reported a treatment effect as measured on the ADAS-Cog of MD -2.48 (95% CI -3.23 to -1.73, 4 studies), which is comparable to the treatment effect reported in this review.

AUTHORS' CONCLUSIONS

Implications for practice

In people with mild, moderate or severe dementia due to Alzheimer's disease treated for periods of 12, 24 and 52 weeks, donepezil at a dose of 10 mg/day produced improvements in cognitive function, measuring -2.9 points as a weighted mean (95% confidence interval (CI) -3.6 to -2.2), in the midrange of the 70-point ADAS-Cog Scale (moderate-quality evidence). Study clinicians, blind to other measures, rated global clinical state more positively in treated participants. Benefits of treatment were also seen on measures of activities of daily living and behaviour. Benefits on the 10 mg/day dose were only marginally larger than on the 5 mg/day dose.

Implications for research

Important emerging issues are the economic effectiveness of the cholinesterase inhibitors. It would be helpful to see long-term randomised studies of treatments that examine real-world economic outcomes, such as cost of care, effects on markers of biological disease progression and the time to and need for institutionalisation. Unfortunately, given the proven clinical efficacy of donepezil it is hard to see how long-term, placebo-controlled randomised studies with economic primary outcomes could now be ethically undertaken.

Further important issues are duration of treatment, the severity of dementia and the effects of withdrawal at the end of the treatment period. As this review has evolved, the evidence of effectiveness of treatment has now been extended to 52 weeks, but effectiveness for some patients may not end at this point. Randomised studies of treatment involving the use of placebos over many years are unlikely to be either a practical or ethical option. Other robust trial designs will be needed to help establish the maximum duration of treatment, and the indicators that treatment is no longer beneficial. There is no evidence to suggest that the effects of donepezil are any less for those with severe dementia.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AD2000

Methods	Double-blinded, placebo-controlled, part cross-over, part parallel-group, randomised trial 60 weeks
Participants	Setting: UK, multicentre Sample size: 566 participants (female, male) Age: Inclusion criteria: • diagnosis of AD with or without vascular dementia, based on DSM-IV • mild-moderate severity • MMSE 10-26 • not in residential care • a regular carer Exclusion criteria: • major life-threatening disease other than dementia
Interventions	• Placebo • Donepezil 5 mg/d • Donepezil 5 mg/d or 10 mg/d (after 12 weeks)

Outcomes	• Cognitive function
	  ○ MMSE
	• ADL
	  ○ Bristol ADL Scale
	• Behavioural symptoms
	  ○ NPI
	• CGIC
	• Other scales:
	  ○ GHQ-30

Source of funding	NHS Executive R&D (West Midlands)
Declaration of interest	Reported
Notes	Initially participants randomised to placebo or 5 mg/d donepezil. After 12 weeks participants randomised again to placebo, 5 mg/d or 10 mg/d. In addition suitable participants were randomised to aspirin or aspirin avoidance. After 60 weeks, following a washout period, there was an option of open-label treatment

Risk of bias

Bias	Authors' judgement	Support for judgement

AD2000 (*Continued*)

Random sequence generation (selection bias)	Low risk	Telephone randomisation
Allocation concealment (selection bias)	Low risk	Study is described as double blind. At the first randomisation there was little risk of revealing the allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was described as matching
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study is described double blind but no information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	From the first phase, the 12-week phase, 36/282 (36%) withdrew from the donepezil arm, and 18/283 (6%) from the placebo arm
Selective reporting (reporting bias)	Low risk	All assessed outcomes were reported
Other bias	High risk	The participants were randomised at baseline and again at 3 months. On average half of the participants may have changed intervention arm as though in a cross-over trial. This may have affected the blinding

Black 2007

Methods	Double-blind, parallel-group, placebo-controlled, randomised trial 24 weeks
Participants	Setting: Australia, Canada, France, UK, USA, multicentre (98 sites) Sample size: 343 participants (102 men and 241 women) Age: mean age 78.0 (8.2), mean MMSE 7.5 (3.5) Selection criteria: • diagnosis of probable AD, according to the NINCDS-ADRDA criteria and DSM-IV • MMSE 1-12 • FAST $\geq$ 6 • modified Hachinski $\leq$ 6 • controlled conditions (diabetes, hypertension) • certain medications if the dose were stable and established were not excluded Exclusion criteria: • significant other disease, other primary psychiatric disorder • history of alcohol or drug abuse

Black 2007 (*Continued*)

Interventions	• Placebo • Donepezil 5 mg/d for 6 weeks followed by 10 mg/d thereafter

Outcomes	Assessments were made at baseline, 16 and 24 weeks
	• Cognitive function:
	  ○ SIB
	  ○ MMSE
	• ADL:
	  ○ ADCS-ADL-sev
	• Behavioural:
	  ○ NPI
	• CGIC tests:
	  ○ CIBIC-Plus
	• Adverse events
	• Other:
	  ○ RUSP assesses the resources used by the participant
	  ○ CBQ to assess the time and stress associated with assisting the patient

Source of funding	Supported by Eisai Inc. and Pfizer Inc.
Declaration of interest	Reported
Notes	This study investigated the potential treatment benefits of donepezil in community-dwelling people with severe AD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation according to a computerised randomisation schedule generated by Almedica Service Corp
Allocation concealment (selection bias)	Low risk	The labels on the medication kits were attached unopened to the case report form by the study personnel
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo and donepezil tablets were identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals 59/176 in donepezil group (43 due to adverse events), 40/167 (18 due to adverse events) in placebo group

Black 2007 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other source of bias expected

Burns 1999

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 24 weeks
Participants	Setting: Australia, Canada, Europe, New Zealand and South Africa, multicentre (82 sites) Sample size: 818 participants, 348 men and 470 women Age: mean age 71.7 (8.3) MMSE: mean MMSE 20.2 (5.0) Inclusion criteria: • diagnosis of probable AD, according to the NINCDS-ADRDA criteria and DSM-III-R categories 290.00 and 290.10 • no clinical or laboratory evidence of a cause other than AD for their dementia • MMSE 10-26 • CDR = 1 (mild dementia) or 2 (moderate dementia) • caregiver • CT or MRI within 6 months of entry Exclusion criteria: • evidence of insulin-dependent diabetes mellitus or other endocrine disorder • asthma, obstructive pulmonary disease • clinically significant uncontrolled gastrointestinal hepatic or cardiovascular diseases • hypersensitivity to cholinesterase inhibitors • tacrine or other investigational medicines within 1 month of baseline • concomitant medications such as anticholinergics, anticonvulsants, antidepressants and antipsychotics • drugs with CNS activity were prohibited or partially restricted
Interventions	• Placebo • Donepezil 5 mg/d • Donepezil 10 mg/d
Outcomes	Assessments at weeks 3, 6, 12, 18, 24 weeks and follow up at 30 weeks • Cognitive function ○ ADAS-Cog • ADL ○ Interview for Deterioration in Daily living in Dementia scale (IDDD) (functional evaluations) • CGIC tests ○ CIBIC-Plus ○ CDR-SB (CDR sum of boxes) • Other ○ QoL

Burns 1999 (*Continued*)

	• Adverse events
Source of funding	Eisai Inc.
Declaration of interest	None reported
Notes	Participants in the 10 mg/d group received 5 mg/d for the 1st week of treatment. 6-week placebo washout phase followed the double-blind phase The group on 10 mg/d of donepezil was on a blinded forced titration scheme of 5 mg/d for week 1, and 10 mg/d for the remainder of the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The participant-randomisation schedule was computer-generated by Univial Europe Ltd
Allocation concealment (selection bias)	Low risk	Univial Europe and Eisai both maintained sealed envelopes containing the master randomisation list, which was only to be opened in a medical emergency
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical appearance of 7.2 mm, film-coated tablets for all groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding was maintained at all times, apart from one medical emergency
Incomplete outcome data (attrition bias) All outcomes	Low risk	23% of participants discontinued from the study, 20% in the placebo group, 22% in the 5 mg/d group, and 26% in the 10 mg/d group
Selective reporting (reporting bias)	Low risk	Data were available on all outcomes.
Other bias	Low risk	No other source of bias anticipated

Farlow 2010

Methods	Double-blinded, 2-arm, parallel-group randomised trial 24 weeks of treatment
Participants	Setting: 219 sites in Asia, Europe, Australia, North America, South Africa, and South America

Farlow 2010 (*Continued*)

	Sample size: 1467 participants (63% female, 37% male) Age: mean age 73.9 (SD = 8.5) Inclusion criteria: • DSM-IV, NINCDS-ADRDA criteria for probable AD • MMSE 0-20 • SIB ≤ 90 • Cornell scale for depression < 12 • 45-90 years old • most comorbidities if the condition stable and well controlled • receiving single daily dose of donepezil 10 mg for ≥ 12 weeks • MRI or CT scan within one year of screening to rule out other causes of dementia Exclusion criteria: • additional neurological disorder • other anticholinergic drugs
Interventions	• Donepezil single daily dose 10 mg • Donepezil sustained release (SR) single daily dose 23 mg Participants were randomly assigned in a 1:2 ratio (10 mg to 23 mg)

Outcomes	Assessments made at baseline, 3, 6, 12, 18 and 24 weeks
	• Cognitive function
	  ○ SIB
	  ○ MMSE
	  ○ ADAS-Cog
	• ADL
	  ○ ADCS-ADL-sev
	• CGIC tests:
	  ○ CIBIC+
	• Adverse events

Source of funding	Eisai Inc
Declaration of interest	The study authors reported receiving research funding from various pharmaceutical companies
Notes	The objective of this study was to compare the effectiveness and safety profile of high-dose donepezil (23mh/d) and standard dose donepezil (10 mg/d) in participants with moderate-severe AD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned using computer-generated randomisation codes
Allocation concealment (selection bias)	Low risk	Participants, caregivers and study personnel were blinded to treatment assignment

Farlow 2010 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Because the treatments were not identical in appearance, a double-dummy design was used to maintain blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No further information but likely to be adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	296/981 (30%) discontinued in the 23 mg/d arm, 87/486 (18%) in the 10 mg/d arm
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Reporting according to CONSORT statement and no other source of bias anticipated

Feldman 2001

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 24 weeks
Participants	Setting: Australia, Canada, France, multicentre (32 sites) Sample size: 292 participants, 115 men and 177 women Age: aged 51-94 years Inclusion criteria: • diagnosis of probable or possible AD, of moderate or severe severity, according to the NINCDS-ADRDA criteria • no clinical or laboratory evidence of a cause other than AD for dementia • MMSE 5-17 • reliable caregiver • FAST $\leq$ 6 Exclusion criteria: • delirium, depression or other illness that may interfere with the study • other neurologic or psychiatric diagnosis • history of drug or alcohol misuse • hypersensitivity to AChE inhibitors • clinically obstructive airway disease, asthma, haematologic or oncologic disorder within last 2 years • B12 or folate deficiency • active gastrointestinal, renal, hepatic, endocrine or cardiovascular system disease Most concomitant medications were allowed except those with notable cholinomimetic or anticholinergic effects
Interventions	• Placebo • Donepezil 10 mg/d

Feldman 2001 (*Continued*)

Outcomes	Assessments were carried out at 4, 8, 12, 18 and 24 weeks
	• Cognitive function:
	  ○ MMSE
	  ○ SIB
	• ADL:
	  ○ DAD
	  ○ IADL
	  ○ PSMS
	  ○ FRS
	• CGIC tests;
	  ○ CIBIC+
	• Behavioural symptoms:
	  ○ NPI
	• Adverse events
	• Other:
	  ○ FRS
	  ○ CSS
	  ○ SF-36
	  ○ CAUST

Source of funding	Pfizer Inc. and Eisai Inc.
Declaration of interest	None reported
Notes	The group on donepezil took 5 mg/d for the first 4 weeks, followed by 10 mg/d for 20 weeks. The dose could be reduced to 5 mg/d at any point if necessary

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation scheme
Allocation concealment (selection bias)	Low risk	Participants, caregivers and study personnel were blinded to treatment assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical film-coated tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blinded, no further information but probably done adequately
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar numbers were lost to follow-up from both groups, 20/146 withdrew from the placebo group and 23/144 from the

Feldman 2001 (*Continued*)

		donepezil group
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	Reported according to the CONSORT statement and no other source of bias anticipated

Hegerl 2003

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 12 weeks
Participants	Setting: Germany Sample size: 40 participants Inclusion criteria: • probable AD according to DSM-IV and NINCDS-ADRDA Exclusion criteria: • any medication known to produce extrapyramidal symptoms
Interventions	• Placebo • Donepezil 10 mg/d
Outcomes	• 1. Cognitive function: ○ ADAS-Cog • 2. Other ○ hand-motor evaluation
Source of funding	Pfizer Inc. and Eisai Europe
Declaration of interest	None reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Described as randomised, double blind, probably adequate
Allocation concealment (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate

Hegerl 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Not reported according to CONSORT guidelines

Homma 1998

Methods	Randomised, double-blind, parallel-group, placebo-controlled study 12 weeks
Participants	Setting: Japan, multicentre (55 sites) Sample size: 190 participants Inclusion criteria: • diagnosis of AD, according to the NINCDS-ADRDA and DSM-III-R criteria • CT, MRI or SPECT examination • Hachinski ischaemic score < 5 • CDR < 3 (mild-moderate AD dementia), made over a period of 4 weeks prior to entry Exclusion criteria: • localised brain lesion or multiple infarctions confirmed by CT or other image diagnoses • visual or auditory impairment • aphasia or other disability that prevented compliance with test procedures • other neurological disorder • due to be admitted to hospital • consciousness disturbance with history of head-trauma • > 85 years • history of hypersensitivity to drugs • confined in bed • hepatic, renal or cardiac disorders
Interventions	• Placebo • Donepezil 3 mg/d • Donepezil 5 mg/d

Outcomes	• Cognitive function
	  ○ ADAS-Jcog
	• ADL
	  ○ Crichton
	• CGIC tests:
	  ○ CDR-SB

Homma 1998 (*Continued*)

	○ MENFIS ○ FGIR ○ GIR
Source of funding	No information
Declaration of interest	No information
Notes	The tablets were sent to the sites as units of 3 cases (3 mg, 5 mg and placebo) of concealed identity

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Homma 2000

Methods	Randomised, double-blind, parallel-group, placebo-controlled study 24 weeks
Participants	Setting: Japan, multicentre (54 sites) Sample size: 268 participants (67% female) Age: mean age 69.8 (8.2) Inclusion criteria: • diagnosis of AD, according to the DSM-IV criteria • CT, MRI or SPECT examination • Hachinski ischaemic score < 5 • CDR of < 3 (mild-moderate AD dementia), made over a period of 4 weeks prior to entry

Homma 2000 (*Continued*)

	• MMSE 10-26 • ADAS-Jcog ≥ 15 Exclusion criteria: • localised brain lesion or multiple infarctions confirmed by CT or other image diagnoses • visual or auditory impairment • aphasia or other disability that prevented compliance with test procedures • other neurological disorder • consciousness disturbance with history of head-trauma • symptoms of depression • no carer • peptic ulcer • serious medical complications Use of choline activators, anticholinergics, cerebral vasodilators, activators of cerebral metabolism, psychotropic drugs, hypnotics, antiparkinsonism agents and nonsteroidal anti-inflammatory drugs prohibited during the trial period
Interventions	• Placebo • Donepezil 5 mg/d
Outcomes	• Cognitive function: ○ ADAS-Jcog • ADL ○ Modified Crichton Scale • CGIC tests: ○ CDR-SB ○ MENFIS ○ Japanese CGIC
Source of funding	No details
Declaration of interest	None reported
Notes	To avoid gastrointestinal problems the donepezil dose was 3 mg/d for the first week

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of randomisation
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information

Homma 2000 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	18/134 withdrew from the donepezil group and 17/129 from the placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	No information

Homma 2008

Methods	Double-blind, parallel-group, placebo-controlled, randomised trial 24 weeks
Participants	Setting: Japan (multicentre) Sample size: 302 participants (20% men) with severe AD, Age: mean 78.2 (8.0) years , mean MMSE 7.8 (3.5) Inclusion criteria: • diagnosis of probable AD, according to the DSM-IV • diagnosis confirmed by a CT or MRI scan • MMSE 1-12 • FAST $\geq$ 6 • modified Hachinski $\leq$ 6 • residing in the community • aged > 50 years • people with controlled conditions (diabetes, hypertension) were not excluded • people taking certain medications if the doses were stable and established were not excluded Exclusion criteria: • significant other disease • other primary psychiatric disorder
Interventions	• Placebo • Donepezil 5 mg/d • Donepezil 10 mg/d The dose was escalated in the donepezil groups

Outcomes	Assessments were carried out at baseline, weeks 8, 16, and 24
	• Cognitive function
	  ○ SIB
	• ADL
	  ○ ADCS-ADL-sev
	• Behavioural
	  ○ BEHAVE-AD
	• CGIC tests

Homma 2008 (*Continued*)

	○ CIBIC+ ● Adverse events
Source of funding	Not reported
Declaration of interest	None reported
Notes	This study was conducted to assess the efficacy and safety of donepezil in Japanese patients with severe AD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised by a computerised randomisation schedule
Allocation concealment (selection bias)	Low risk	Allocation carried out independently of all parties in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching donepezil and placebo tablets, identical in appearance, taste and smell
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind, no further details were reported but methods probably adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	The discontinuation rate due to adverse events and illness were 10.5% in the placebo group, 7.9% in the 5 mg group, and 13.5% in the 10 mg group
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	Does not appear to be reported according to CONSORT guidelines but no other source of bias anticipated

Homma 2016

Methods	Double-blind, parallel-group, randomised trial 24 weeks
Participants	Setting: 69 sites in Japan Sample size: 351 participants (69% female, 31% male) Age: mean age 76.0 (SD = 8.8) Inclusion criteria:

Homma 2016 (*Continued*)

	• DSM-IV-TR, NINCDS-ADRDA criteria for probable AD • MMSE 1-12 • SIB 10-90 at screening and baseline • age ≥ 50 years old • most comorbidities if the condition stable and well controlled • receiving single daily dose of donepezil 10 mg for ≥ 12 weeks • MRI or CT scan within 1 year of screening to rule out other causes of dementia • outpatients or in nursing home • caregiver who will provide informed consent separately for own participation in study Exclusion criteria: • additional neurological disorder • other anticholinergic drugs
Interventions	• Donepezil single daily dose 10 mg • Donepezil SR single daily dose 23 mg Participants were randomly assigned in a 1:2 ratio (10 mg to 23 mg)

Outcomes	Assessments made at baseline, 3, 6, 12, 18 and 24 weeks
	• Cognitive function
	  ○ SIB
	• CGIC tests:
	  ○ CIBIC+
	• Adverse events

Source of funding	Not reported
Declaration of interest	The study authors reported receiving research funding from various pharmaceutical companies
Notes	The objective of this study was to compare the effectiveness and safety profile of high-dose donepezil (23 mg/d) and standard dose donepezil (10 mg/d) in people with moderate-severe AD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation scheme
Allocation concealment (selection bias)	Low risk	Study described as double-blinded, no further details given, but methods probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo tablets were used in both groups together with the active tablets to blind allocation. Tablets not described as identical but blinding was probably adequate

Homma 2016 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study described as double-blinded, no further details given, but methods probably adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very few participants were lost to follow-up. Sensitivity analyses carried out to assess the effect of non completers
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Unclear whether CONSORT guidelines followed but no other source of bias anticipated

Howard 2007

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 12 weeks
Participants	Setting: England, UK, 8 centres Sample size: 259 participants, 15% male Age: mean age 84.5 (8.0) MMSE: mean MMSE 8.2 (6.5) Inclusion criteria: • diagnosis of probable AD, according to the NINCDS-ADRDA • clinical agitation causing distress to patient and carer, that had not responded to psychological treatment • at least moderate management problems • living in a residential home or with a carer • CMAI ≥ 39 • age > 39 years Exclusion criteria: unstable, uncontrolled medical conditions
Interventions	• Donepezil 10 mg/d • Placebo
Outcomes	Assessments at weeks 4 and 12 • cognitive function: ○ SIB ○ MMSE • CGIC tests: ○ CGIC • Behavioral symptoms: ○ total CMAI ○ NPI • Adverse events • Other: ○ NPI-D (caregiver distress scale)

Howard 2007 (*Continued*)

Source of funding	Supported by Grants from the MRC and the Alzheimer's Society. Donepezil was provided by Eisai UK
Declaration of interest	These were reported.
Notes	The trial was planned with a third group taking risperidone, but this was abandoned after 13 participants had been randomised to this arm, after warnings had been issued by the UK Committee for Safety of Medicines that risperidone and olanzapine were not be used for the treatment of behavioral symptoms in dementia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Telephone randomisation centrally by MRC Clinical Trials Unit
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study medication was encapsulated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinicians, patients, carers and assessors were all unaware of the treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	13/128 were lost to follow-up from the donepezil group, and 19/131 from the placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Study was reported according to CONSORT guidelines and no other sources of bias anticipated

Jia 2017

Methods	Double-blind, parallel-group, randomised trial 24 weeks
Participants	Setting: 38 hospitals in China Sample size: 313 participants (65% female, 35% male) Age: mean age 70.8 (SD = 9.6) Inclusion criteria: • DSM-IV-TR, NINCDS-ADRDA criteria for probable AD • MMSE 1-12

Jia 2017 (*Continued*)

	• SIB 10-90 at screening and baseline • age 50-90 years old • most concomitant medications were allowed • MRI or CT scan to confirm diagnosis • caregiver Exclusion criteria: • additional neurological disorder • other anticholinergic drugs
Interventions	• Placebo • Donepezil 10 mg/d in one dose Titration at 6 weeks from 5 mg/d

Outcomes	Assessments made at baseline, 6, 12, 18 and 24 weeks
	• Cognitive function
	  ○ SIB
	  ○ MMSE
	• CGIC tests:
	  ○ ADCS-CGIC
	• Adverse events

Source of funding	Donepezil was provided by Eisai China
Declaration of interest	Reported
Notes	No down-titration to a previous dose was allowed for those who could not tolerate the study drug

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants randomised by a computerised randomisation schedule generated by staff independent of study in other respects
Allocation concealment (selection bias)	Low risk	Allocation carried out independently of all parties in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The placebo and donepezil tablets (5 mg and 10 mg) were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants, caregivers, site investigators, and the sponsor were blind to the treatment allocation

Jia 2017 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	30/156 withdrew from the placebo arm (10 adverse events, 5 protocol violations, 6 withdrew consent, 2 lost to follow-up, 7 others), 29/157 in the donepezil arm (14 due to adverse events, 3 protocol violations, 3 lost to follow-up, 6 withdrew consent, and 3 others)
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	There is no explicit statement that CONSORT reporting guidelines were used, but the report follows these

Krishnan 2003

Methods	Randomised, double-blind, parallel-group, placebo-controlled study 24 weeks
Participants	Setting : USA, 3 centres Sample size: 67 participants (48 women, 19 men) Age: mean age 73.4 years Inclusion criteria: • mild-moderate AD, according to DSM-IV-R and NINCDS-ADRA • MMSE 10-26 • CDR = 1 or 2 • Hachinski score ≤ 4 • able to undergo MRI scan Exclusion criteria: • psychiatric disorder other than AD • cerebrovascular disease • concomitant psychotropic drugs
Interventions	• Placebo • Donepezil 10 mg/d
Outcomes	• 1. Cognitive function: ○ ADAS-Cog
Source of funding	Eisai Inc. and Pfizer Inc.
Declaration of interest	Reported
Notes	The MRI study Primary outcomes were neuronal markers and hippocampal volumes
Risk of bias	

Krishnan 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation schedule
Allocation concealment (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical donepezil and placebo tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	67 participants enrolled. In the placebo group 10/33 withdrew, and in the donepezil group 6/34 withdrew before end of treatment
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other source of bias anticipated

Lebert 1999

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 12 weeks
Participants	Setting: unknown multicentre (53 sites) Sample size: 318 participants Age: mean age 72 years Inclusion criteria: • Mild AD based on DSM-IV and NINCDS-ADRDA criteria • MMSE 18-26
Interventions	• Placebo • Donepezil 10 mg/d

Outcomes	• Cognitive function:
	  ○ modified ISAAC test
	  ○ cued recall memory test
	  ○ Benton test of recognition
	  ○ trail making test
	  ○ digit cancellation test
	  ○ span test
	  ○ naming test

Lebert 1999 (*Continued*)

	• ADL:
	  ○ Lawton ADL
	  ○ NOSGER
	• CGIC tests:
	• Behavioural symptoms:
	  ○ NPI
	• Other:
	  ○ aRSS (abridged relative's stress scale)

Source of funding	Eisai SA
Declaration of interest	None reported
Notes	1/3 randomised to placebo, 2/3 to donepezil 4-week titration on 5 mg/d before increasing to 10 mg/d. 5 participants were mis-randomised

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers who withdrew were not reported
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	High risk	Information is confined to a number of conference abstracts, which showed inconsistent reporting

Maher-Edwards 2011

Methods	Double-blinded, placebo-controlled, randomised trial 24 weeks
Participants	Setting: 24 centres in Austria, Bulgaria, Chile, Estonia, Germany, the Russian Federation, Slovakia, and the UK Sample size: 130 participants (33% male, 76% female) Age: mean age 71.2 (7.8) years inclusion criteria: • age 50-85 years • diagnosis of probable AD according to DSM_IV and NINCDS-ADRDA criteria • MMSE 12-24 • living in the community Exclusion criteria: • vascular dementia • significant psychiatric illness • history of seizures • another cholinesterase inhibitor, memantine, selegiline within 3 months of baseline • antipsychotic medication • barbiturates
Interventions	• Placebo • Donepezil 10 mg/d in one dose Titration at 4 weeks from 5 mg/d

Outcomes	Assessments at baseline, weeks 8, 16 and 24
	• Cognitive function
	  ○ ADAS-Cog
	• ADL
	  ○ DAD
	• Behavioral symptoms
	  ○ NPI
	• CGIC tests
	  ○ CIBIC+
	• Adverse events
	• Other
	  ○ ACQLI

Source of funding	GlaxoSmithKline
Declaration of interest	None declared
Notes	This was a 3-arm trial. The third arm (n = 68) was an experimental drug SB-742457, the results of which were not relevant for this review

Risk of bias

Bias	Authors' judgement	Support for judgement

Maher-Edwards 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	A permutated block randomisation schedule was generated by GlaxoSmithKline
Allocation concealment (selection bias)	Low risk	Study described as double-blinded, no further details given, but methods probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules were described as maintaining the blindness of the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The CIBIC+ was rated by an independent rater with no access to other study information
Incomplete outcome data (attrition bias) All outcomes	Low risk	15/63 withdrew from the placebo arm (1 adverse event, 2 protocol violations, 8 withdrew consent, 4 other), 10/67 in the donepezil arm (4 due to adverse events,1 lost to follow-up, 3 withdrew consent, 1 for non-compliance and 1 other)
Selective reporting (reporting bias)	High risk	Descriptive results only for some outcomes, which were reported to show no treatment effect
Other bias	Low risk	No CONSORT checklist but no other source of bias anticipated

Mazza 2006

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 24 weeks
Participants	Setting: Italy Sample size: 51 participants (54 % female) Age: Inclusion criteria: • diagnosis of probable AD, according to the DSM-IV • Brieg Cognitive Rating Scale 3-5 • Hachinski Ischemic Score < 4 • MMSE 13-25 • SKT 8-23 • pre-morbid IQ > 80 • aged 50-80 years Exclusion criteria: • other causes of depression • severe organic disease

	• history of schizophrenia • Geriatric Depression scale < 11
Interventions	• Donepezil 5 mg/d • Placebo

Outcomes	• Cognitive function:
	  ○ SKT
	  ○ MMSE
	• CGIC tests:
	  ○ CGI

Source of funding	Independent, no conflict of interest declared
Declaration of interest	None reported
Notes	There was a 3rd arm to the trial (n = 25), testing *Ginkgo biloba* special extract. The main aim of the trial was to compare *Ginkgo biloba* with donepezil and with placebo.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	High risk	No information on the blinding of the placebo, donepezil capsules
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This was carried out by researchers who had previously not been involved in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/25 withdrew from the donepezil group, 6/26 from the placebo group
Selective reporting (reporting bias)	Low risk	Results of all outcomes were reported
Other bias	Low risk	No CONSORT checklist but no other source of bias anticipated

Mohs 2001

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 54 weeks
Participants	Setting: USA, multicentre (31 sites) Sample size: 431 participants, 160 men and 271 women with mild-moderately severe AD, mean age 75.4 (8.8), mean MMSE 17.1 (3.0) Inclusion criteria: • diagnosis of probable AD, according to the NINCDS-ADRDA criteria and DSM-IV • MMSE 12-20 • modified Hachinski Ischaemia score ≤ 4 • able to perform 8 of 10 instrumental ADL and 5 of 6 basic ADL (each score ≤ 2) on the ADFACS • carer Exclusion criteria: • evidence of other neurologic or psychiatric disorder • dementia complicated by organic disease • delirium • depression • delusions • History of alcoholism or drug abuse • hypersensitivity to cholinesterase inhibitors • taken tacrine or other investigational medicines within 1 month of baseline • concomitant medications such as anticholinergics, cholinomimetics, tricyclic antidepressants, antiparkinsonian agents and neuroleptics
Interventions	• Placebo • Donepezil 5 mg/d for 28 days followed by 10 mg/d thereafter

Outcomes	• Cognitive function:
	  ○ MMSE
	• ADL:
	  ○ ADFACS
	• CGIC tests
	  ○ CDR-SB (CDR sum of boxes)

Source of funding	Eisai Inc. Pfizer Inc.
Declaration of interest	Reported
Notes	At each visit participants who had met predefined criteria for clinically evident decline in functional status were discontinued

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomisation schedule

Mohs 2001 (*Continued*)

Allocation concealment (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All assessments were carried out by investigators who were blind to the participant's treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The difference in rates of withdrawals before the end of treatment between the groups was small
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Participants were withdrawn if they met predefined deterioration criteria

Moraes 2006a

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 12 weeks
Participants	Setting: Brazil Sample size: 23 participants (65% female) Age: mean age 74.6 years Inclusion criteria: • mild-moderate AD according to ADRDA • sleep apnoea • CDR = 1 or 2 Exclusion criteria: • other causes of dementia • other severe medical or psychiatric conditions
Interventions	• Donepezil 10 mg/d • Placebo
Outcomes	ADAS-Cog
Source of funding	Fundação de Amparo à Pesquisa do Estado de São Paulo and Associação Fundo de Incentivo à Psicofarmacologia
Declaration of interest	There were no conflicts of interest to declare.
Notes	The primary purpose of the trial was to investigate sleep apnoea, and the polysomnography formed the primary outcomes

Moraes 2006a (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number list was generated using Statistica
Allocation concealment (selection bias)	Unclear risk	A randomised number list was used but there were no further details of the administration of the list
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blinded to participants' conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	There appear to be no withdrawals from the study.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Low risk	No CONSORT checklist but no other source of bias anticipated

Moraes 2006b

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 26 weeks
Participants	Setting: Brazil Sample size: 35 participants (69% female) Age: mean age 75.9 years Inclusion criteria: • mild-moderate AD according to ADRDA • CDR = 1 or 2 Exclusion criteria: • other causes of dementia • other severe medical or psychiatric conditions
Interventions	• Donepezil 10 mg/d • Placebo
Outcomes	• Cognitive function: ◦ ADAS-Cog

Moraes 2006b (*Continued*)

Source of funding	This was not an industry-supported study. Fundação de Amparo à Pesquisa do Estado de São Paulo and Associação Fundo de Incentivo à Psicofarmacologia
Declaration of interest	There are no financial conflicts
Notes	The primary purpose of the trial was to investigate rapid eye movement (REM) sleep, and the polysomnography forms the primary outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	No computer-generated randomisation code reported but probably adequate
Allocation concealment (selection bias)	Low risk	The allocation was carried out blinded to treatment code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Wyeth-Whitehall laboratories produced both the placebo and donepezil tablets in a coded form
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blind to participants' conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals from treatment
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No CONSORT checklist but no other source of bias anticipated

Rogers 1996

Methods	Double-blind, randomised, parallel-group, placebo-controlled trial 12 weeks
Participants	Setting: USA (multicentre) Sample size: 161 participants (64 men, 97 women) Age: mean 71.8 years, range 55-85 years Inclusion criteria: • diagnosis of mild-moderately severe AD, according to the NINCDS criteria and DSM-III-R made at least 1 year prior to entry • supported by evidence from CT or MRI studies during 6 months prior to entry • MMSE 10-26 • CDR = 1 (mild dementia) or 2 (moderate dementia)

	• all participants were fully ambulatory or able to walk with an aid and had vision and hearing sufficient for compliance with test procedures Exclusion criteria: • any form of diabetes, obstructive pulmonary disease, haematological or oncological disorder of recent onset, or vitamin B12 or folate deficiency • clinically significant uncontrolled gastrointestinal, renal, hepatic, endocrine or cardiovascular diseases • known hypersensitivity to cholinesterase inhibitors or had taken other investigational medicines within 1 month of baseline • history of alcohol or drug abuse
Interventions	• Placebo • Donepezil 1 mg/d • Donepezil 3 mg/d • Donepezil 5 mg/d
Outcomes	Assessments at baseline, 1, 3, 6, 9, 12 and 14 weeks • Cognitive function ○ ADAS-Cog ○ MMSE • ADL ○ UADL (Uniform ADL) • CGIC tests: ○ CDR-SB (Clinical dementia scale, sum of boxes) ○ CGIC (including caregiver information) • Adverse events • Other: ○ QoL (patient-rated) ○ QoL (carer-rated)
Source of funding	No information
Declaration of interest	No information
Notes	The double-blind phase was followed by a 2-week single-blind placebo washout phase The dose ranging study was undertaken to explore the potential efficacy and safety of donepezil in people with AD, and to examine the relationships between plasma donepezil concentration, red blood cell AChE activity and clinical response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of randomisation procedure
Allocation concealment (selection bias)	Unclear risk	No details given

Rogers 1996 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/39 participants withdrew from the intervention arm (3 for adverse events, 1 for protocol violation and 1 by request), and 5/40 from the placebo arm (2 for adverse events, 3 for protocol violation), before endpoint
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No additional sources of bias expected

Rogers 1998a

Methods	Randomised, double-blind, parallel-group, placebo-controlled study 12 weeks
Participants	Setting: USA, multicentre (23 sites) sample size: 468 participants, 171 men and 297 women Age: aged 50-94 years Selection criteria: • diagnosis of probable AD, according to the NINCDS-ADRDA criteria and DSM-III-R categories 290.00 and 290.10 • age ≥ 50 years • no clinical or laboratory evidence of a cause other than AD for dementia • MMSE 10-26 • CDR = 1 (mild dementia) or 2 (moderate dementia) • ambulatory with or without an aid • sufficient vision and hearing to comply with study procedures Exclusion criteria: • evidence of insulin-dependent diabetes mellitus, asthma, obstructive pulmonary disease haematological or oncological disorder in the previous 2 years • clinically significant uncontrolled gastrointestinal, renal, hepatic, endocrine or cardiovascular diseases • hypersensitivity to cholinesterase inhibitors • other investigational medicines within 1 month of baseline • concomitant medications such as anticholinergic, antianxiety, anticonvulsant, antidepressant, antipsychotic or stimulating agents • evidence of other psychiatric or neurological disorders (stroke, schizophrenia or Parkinson's disease) • Hachinski Ischaemic score ≥ 5

Rogers 1998a (*Continued*)

Interventions	• Placebo • Donepezil 5 mg/d • Donepezil 10 mg/d

Outcomes	• Cognitive function:
	  ○ ADAS-Cog
	  ○ MMSE
	• CGIC tests
	  ○ CIBIC+ (including caregiver information)
	  ○ CDR-SB (Clinical dementia scale, sum of boxes)
	• Adverse events
	• Other:
	  ○ QoL (patient-rated)

Source of funding	Eisai Inc.
Declaration of interest	None reported
Notes	The group on 10 mg/d of donepezil was on a blinded, forced titration scheme of 5 mg/d for week 1, and 10 mg/d for the remainder of the study. Measures of clinical outcome were assessed at baseline and at 3-week intervals. At the end of the double-blind treatment all participants began a 3-week single-blind washout period with placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Allocation concealment (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	93% of participants in the placebo group completed the trial, 90% of the 5 mg/d donepezil group and 82% of the 10 mg/d donepezil group
Selective reporting (reporting bias)	Low risk	All outcomes were reported

Rogers 1998a (*Continued*)

Other bias	Low risk	No other source of bias anticipated

Rogers 1998b

Methods	Randomised, double-blind, parallel-group, placebo-controlled study 24 weeks
Participants	Setting: USA, multicentre (20 sites) Sample size: 473 participants, 180 men and 293 women age: mean age 73.4 years Inclusion criteria: • diagnosis of uncomplicated AD, according to the NINCDS-ADRDA criteria and DSM-III-R categories 290.00 and 290.10 • no clinical or laboratory evidence of a cause other than AD for dementia • MMSE 10-26 • CDR = 1 (mild dementia) or 2 (moderate dementia) • All participants had a reliable caregiver Exclusion criteria: • evidence of insulin-dependent diabetes mellitus or other endocrine disorder • asthma, obstructive pulmonary disease • clinically significant uncontrolled gastrointestinal hepatic or cardiovascular diseases • participants known to be hypersensitive to cholinesterase inhibitors or who had taken tacrine or other investigational medicines within 1 month of baseline • concomitant medications such as anticholinergics, anticonvulsants, antidepressants and antipsychotics were not allowed • drugs with central nervous system activity were prohibited or partially restricted
Interventions	• Placebo • Donepezil 5 mg/d • Donepezil 10 mg/d
Outcomes	• Cognitive function: ○ ADAS-Cog ○ MMSE • CGIC: ○ CIBIC plus (including caregiver information) ○ CDR-SB (Clinical dementia scale, sum of boxes) • Other: ○ QoL (patient-rated)
Source of funding	Eisai Inc
Declaration of interest	None reported
Notes	The group on 10 mg/d of donepezil was on a blinded, forced titration scheme of 5 mg/d for week 1, and 10 mg/d for the remainder of the study. Measures of clinical outcome were assessed at baseline and at 6-week intervals

Rogers 1998b (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomisations schedule was used
Allocation concealment (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	80% of participants in the placebo group completed the trial, 85% of the 5 mg/d donepezil group and 68% of the 10 mg/d donepezil group
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other source of bias anticipated

Schindler 2004

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 24 weeks
Participants	31 participants with mild-moderate AD (MMSE 10-26) currently taking 10 mg/d donepezil
Interventions	• Placebo • Donepezil 10 mg/d
Outcomes	TEAEs
Source of funding	No information
Declaration of interest	No information
Notes	Participants randomised to the treatment group took a further 5 mg/d of donepezil for 12 weeks, followed by a further 5 mg/d for weeks 12-24

Schindler 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Seltzer 2004

Methods	Double-blind, parallel-group, placebo-controlled, randomised trial 24 weeks
Participants	Setting: USA, multicentre (17 sites) Sample size: 153 participants, 71 men and 82 women Age: mean age 74.0 years Inclusion criteria: • probable AD diagnosed within the last year (DSM-IV and NINCDS-ADRDA) • MMSE 21-26 (mean MMSE = 24.1) • modified Hachinski ≤ 4 • CDR 0.5 or 1.0 • only mild impairment of ADL Exclusion criteria: • memory impairment due to stroke or Parkinson's disease • previous treatment with cholinesterase inhibitor
Interventions	• Placebo • Donepezil 5 mg/d for 6 weeks followed by forced escalation to 10 mg/d thereafter
Outcomes	Assessments carried out at baseline, 6, 12, 18 and 24 weeks • 1. Cognitive function: ○ ADAS-Cog

	○ MMSE ○ CMBT • 2. CGIC tests: ○ CDR-sum of boxes • 3. Other: ○ apathy scale ○ patient-rated global assessment
Source of funding	Eisai Inc. and Pfizer Inc.
Declaration of interest	Not reported
Notes	Participants unable to tolerate 10 mg/d were dropped from the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Allocation concealment (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	26/96 withdrew from the donepezil group (15 due to adverse events) and 11/57 from the placebo group (5 due to adverse events)
Selective reporting (reporting bias)	High risk	Incomplete reporting of some outcomes
Other bias	High risk	Participants who could not tolerate 10 mg donepezil were discontinued from study

Study 205

Methods	Randomised, double-blind, parallel-group, placebo-controlled study 12 weeks
Participants	Setting: USA Sample size: 12 participants
Interventions	• Placebo • Donepezil 10 mg/d

Outcomes	• Cognitive function:
	  ○ MMSE
	• CGIC:
	  ○ CDR-SB
	• Other:
	  ○ QoL

Source of funding	Not reported
Declaration of interest	Not reported
Notes	The visuospatial attention study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Study 306

Methods	12-week, randomised, double-blind, parallel-group, placebo-controlled study
Participants	Country: Italy 39 participants
Interventions	• Placebo • Donepezil 10 mg/d
Outcomes	ADAS-Cog CDR-SB
Source of funding	Not reported
Declaration of interest	Not reported
Notes	ApoE study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation schedule was computer-generated
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Tariot 2001

Methods	Double-blind, parallel group, placebo-controlled, randomised study 24 weeks
Participants	Setting: USA, multicentre (27 sites) Sample size: 208 participants, 37 men and 171 women Age: mean age 85.7 years

Tariot 2001 (*Continued*)

	Inclusion criteria: • possible or probable AD, or AD with cerebrovascular disease (but not vascular dementia) • MMSE 5-26 inclusive • residence in nursing home • at least one NPI symptom reported at a frequency of at least several times per week Exclusion criteria: • most concomitant medications were allowed except those with significant cholinergic or anticholinergic effects
Interventions	• Placebo • Donepezil 10 mg/d

Outcomes	• Cognitive function:
	  ○ MMSE
	• ADL:
	  ○ PSMS
	• CGIC:
	  ○ CDR-SB
	• behavioural symptoms:
	  ○ NPI-NH

Source of funding	Eisai Inc. Pfizer Inc
Declaration of interest	Reported
Notes	The group on donepezil took 5 mg/d for the first 4 weeks, followed by 10 mg/d for 20 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation schedule
Allocation concealment (selection bias)	Low risk	No treatment codes were broken during the course of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was achieved by using identical-appearing film-coated tablets of donepezil and placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate

Tariot 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	18% of the placebo group and 11% of the donepezil withdrew before end of treatment
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other source of bias anticipated

Tune 2003

Methods	Randomised, double-blind, parallel-group, placebo-controlled study 24 weeks
Participants	Setting: USA Sample size: 28 participants (7 male, 21 female) Age: mean age 72.9 years Inclusion criteria: • mild-moderate probable AD (DSM-IV and NINCDS-ADRDA criteria) • CDR = 1 or 2 • MMSE 10-26 • Hachinski ≤ 4 Exclusion criteria:
Interventions	• Placebo • Donepezil 10 mg/d

Outcomes	Assessments at weeks 6, 12, 18, and 24
	• 1. Cognitive function:
	  ○ ADAS-Cog
	• 2. Behavioural symptoms:
	  ○ NPI

Source of funding	Eisai, Inc.
Declaration of interest	None reported
Notes	Functional brain activity assessed by cerebral glucose metabolism

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Allocation concealment (selection bias)	Low risk	Described as randomised, double-blind, probably adequate

Tune 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 28 participants (14 in each group) were enrolled, and 26 participants completed. Two participants in the placebo group withdrew before end of study
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No additional sources of bias expected

Winblad 2001

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 52 weeks
Participants	Setting: northern Europe, multicentre (28 sites) Sample size: 286 participants, 102 men and 184 women Age: mean age 72.5 years Inclusion criteria: • mild-moderate possible or probable AD • diagnosis of AD with DSM-IV and NINCDS-ADRDA criteria • 9 < MMSE < 27 • CT or MRI within 12 months of baseline • caregiver Exclusion criteria: • clinically significant and unstable, active gastrointestinal, renal, hepatic, endocrine or cardiovascular disease • neurologic or psychiatric disease other than AD • history of alcohol or drug abuse • insulin-dependent diabetes • COPD, asthma
Interventions	• Placebo • Donepezil 10 mg/d

Outcomes	• 1. Cognitive function
	  ○ GBS
	  ○ MMSE
	• 2. ADL
	  ○ PDS
	• 3. CGIC tests

Winblad 2001 (*Continued*)

	○ GBS • 4. Behavioural symptoms ○ NPI • 5. other: ○ GDS
Source of funding	Pfizer Pharmaceuticals Group, Pfizer, Inc.
Declaration of interest	None reported
Notes	The group on donepezil received 5 mg/d for 28 days initially, and then 10 mg/d according to the clinician's judgement for 1 year

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer-generated randomisations list produced by Pfizer, Inc. (NY)
Allocation concealment (selection bias)	Low risk	No information but probably adequate described as double-blinded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No information but probably adequate described as double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information but probably adequate described as double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	47/142 (33%) withdrew from the donepezil group and 47/144 (33%) from the placebo group
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No CONSORT checklist but no other source of bias anticipated

Winblad 2006

Methods	Double-blind, parallel-group, placebo-controlled, randomised study 6 months
Participants	Setting: Sweden, multicentre (50 nursing homes) Sample size: 248 participants, 58 men and 190 women

Winblad 2006 (*Continued*)

	Age: mean age 84.9 years Inclusion criteria: • probable or possible AD (DSM-IV and NINCDS-ADRDA) • MMSE 1-10 • age ≥ 50 years • CT or MRI scan at time of diagnosis • FAST 5-7 Exclusion criteria: • dementia other than AD • primary psychiatric and neurological disorders
Interventions	• Placebo • Donepezil 5 mg/d for 30 days followed 10 mg/d thereafter
Outcomes	• Cognitive function: ○ SIB ○ MMSE • ADL: ○ ADCS-ADL-severe • CGIC tests: ○ CGI-C • Behavioural symptoms: ○ NPI
Source of funding	Pfizer Pharmaceuticals
Declaration of interest	Reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation schedule was generated centrally by the Global Clinical Data Services at Pfizer
Allocation concealment (selection bias)	Low risk	Described as randomised, double-blind, probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as randomised, double-blind, probably adequate

Winblad 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	7% of the placebo group and 16% of the donepezil group withdrew before the end of study
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other source of bias anticipated

Some of the first studies published were identified by their study number, and this has been retained since the first version of this review. **AChE**: acetylcholinesterase; **ACQLI**: Alzheimer Carer's Quality of Life Instrument; **AD**: Alzheimer's disease; **ADAS-Cog**: Alzheimer's Disease Assessment Scale (cognitive);**ADAS-Jcog**: Alzheimer's Disease Assessment Scale (Japanese cognitive);**ADCS-ADL**: Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (severe version); **ADCS-CGIC**: Alzheimer's Disease Cooperative Study - Clinician's Interview-Based Impression of Change; **ADFACS**: AD Functional Assessment and Change Score; **ADL**: Activities of Daily Living; **ADRDA**: ?; **aRSS**: abridged Relative's Stress Scale; **BADLS**: Bristol Activities of Daily Living Scale; **BEHAVE-AD**: Behavioural Pathology in Alzheimer's Disease Rating Scale; **CAUST**: Canadian Utilization of Services Tracking; **CBQ**: Caregiver Burden Questionnaire; **CDR-SB**: Clinical Dementia Scale, sum of boxes; **CGIC**: Clinician's Global Impression of Change; **CIBIC+**: Clinician's Interview-Based Impression of Change;**CMAI**: Cohen-Mansfield Agitation Inventory; **CMCS**: Crichton Scale; **CONSORT**: Consolidated Standards of Reporting Trials; **COPD**: Chronic Obstructive Pulmonary disease; **CSS**: Caregiver Stress Scale; **CT**: computed tomography; **DSM**: Diagnostic and Statistical Manual of Mental Disorders;**DAD**: Disability Assessment for Dementia; **FAST**: Functional Assessment Staging; **GHQ-30**: General Health Questionnaire; **GBS**: Gottfries, Brane and Steen scale; **GDS**: Geriatric Depression Scale **IADL**: Instrumental Activities of Daily Living; **MENFIS**: Mental Function Impairment Scale; **MMSE**: Mini Mental State Examination; **MRC**: Medical research Council; **MRI**: magnetic resonance imaging; **NINCDS-ADRDA**: Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association; **NOSGER**: Nurses' Observation Scale for Geriatric Patients; **NPI**: Neuropsychiatric Instrument; **NPI-D**: Neuropsychiatric Inventory Distress scale; **PDS**: Progressive Deterioration Scale; **PSMS**: Physical Self Maintenance Scale; **QoL**: Quality of Life; **RUD**: Resource Utilization in Dementia; **RUSP**: Resources Utilisation for Severe Alzheimer's Disease Patients; **SIB**: Severe Impairment Battery; **SD**: standard deviation; **SF-36**: Short Form - 36; **SKT**: Syndrom Kurz Test; **SPECT**: single-photon emission computed tomography; **SR**: sustained release; TEAE: treatment-emergent adverse event; **UADL**: Uniform Activities of Daily Living

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ames 2001	Open-label study, one group all on donepezil
AWARE	This is a withdrawal study, the participants had all been taking Donepezil immediately before randomisation
Barak 2001	Open-label study
Berger 2000	Open-label study, one group all on donepezil
Birt 2002	Open-label study

(*Continued*)

Borroni 2001	Open-label study, one group all on donepezil
Brodaty 2000	Open-label study, one group all on donepezil
Bullock 2000	Open-label study, one group all on donepezil
Bullock 2001	Randomised study comparing donepezil with rivastigmine
Cameron 2000	Open-label study carried out in general practice, one group all on donepezil
Clary 2000	Sertraline+donepezil vs donepezil. Study of sertraline not donepezil
Cumbo 2011	Open-label randomised study comparing donepezil with memantine, galantine, and rivastigmine. There was no placebo arm
Cummings 2000	Matched groups, not randomised
DOMINO-AD	The participants were already stable on donepezil. On randomisation memantine was added and in some donepezil withdrawn. Withdrawal studies are not considered in this review
Dong 2011	Donepezil is compared with usual care. This is not a randomsied study
Fillit 2002	Case-control study
Froelich 2000	Open-label, 24-week study, 237 participants from routine clinical practice, all on donepezil (5 mg/dor 10 mg/d)
Fuschillo 2001	Open-label study
Geldmacher 2003	Open-label extension to studies 210, 301 and 302. Reports results of analysis of time to institutionalisation
Ghorbani 2010	This study was not randomised, participants were allocated to study arm by consecutive non-random sampling, and the only outcomes were measures of cerebral blood flow
Greenberg 2000	Duration of treatment in this randomised, cross-over trial was only 6 weeks
Hampel 2002	Retrospective population study
Holmes 2004	This is a withdrawal study, the participants had all been taking Donepezil immediately before randomisation
Homma 1998a	Open-label study
Homma 1998b	Randomisation was not mentioned. The treatment of 2 mg/d was compared with 0.1 mg/d and there was no placebo group
Imai 1998a	Open-label study

(*Continued*)

Imai 1998b	Open study
Imai 1998c	Open study
Janssen 2005 b	Donepezil was compared with galantamine. There is no placebo arm
Kauffer 1998	Open-label study, one group all on donepezil
Kemp 2003	Randomised, placebo-controlled, double-blind study of 12 participants. Brain image outcomes only
Leube 2002	All participants on donepezil. Outcome was change of neural activation measured by functional MRI
Lopez 2008	Open-label study of donepezil with no placebo group
Maltz 2002	Non-randomised study. Outcome was response to methacholine-induced cutaneous vasodilation
Matthews 2000	Open-label study, one group all on donepezil
McRae 1999	Open-label study, one group all on donepezil
McRae 2001a	Retrieval of participants from studies 301 and 302 after treatment ended for follow-up
Mega 1999	Open-label study, one group all on donepezil
Mega 2001	Donepezil vs memantine, matched groups
Mega 2002	Non-randomised study of donepezil, metrifonate or galantamine. Outcome was response to cerebral metabolic activation
Modrego 2010	Donepezil compared with memantine. There was no placebo arm.
NCT00423228-BRAINz	Donepezil was compared with ZT-1, an investigational product. There was no placebo arm
Nikolova 2001	Open-label study, one group all on donepezil
Nobili 2002	Open-label study using retrospective control group. Brain perfusion SPECT and MMSE assessed
Ollat 2007	This RCT had no placebo group.
Onofrj 2002	Small, randomised study comparing donepezil with vitamin E for mild AD and for moderate-severe AD. There was no placebo group. The latency of P300 ERP was the primary outcome, MMSE was a secondary outcome
Onofrj 2003	Small, randomized, cross-over study comparing donepezil with vitamin E. There was no placebo group. The primary outcomes were EEG abnormalities, investigated in those with fluctuating cognition
Parsa 2000	Open-label study, one group all on donepezil+quetiapine

(*Continued*)

Peng 2002	Randomised, placebo-controlled study, but only single-blind
Peng 2005	Single-blind, randomised, placebo-controlled study. Participants were not blinded to treatment
Requena 2006	This 4-group study was not blinded. There was no placebo group
Richarz 2011	Donepezil was compared with galantamine. There was no placebo arm
Rocca 2002	Open-label study, one group all on donepezil
Rockwood 2002	Open-label study, all participants on donepezil
Rockwood 2007	Open-label study, all participants on donepezil
Rodriguez 2002	Open-label study, one group all on donepezil
Rogers 1997	Open-label titration study using placebo participants from a phase III trial
Rogers 1997b	Non-randomised open-label follow-on study
Rozzini 2002	Donepezil compared with rivastigmine
Rozzini 2007a	Open-label study, all participants on donepezil
Rozzini 2007b	Open-label study, all participants on donepezil
Salloway 2002	Donepezil was compared with galantamine. There was no placebo arm
Sampson 2007	Placebo-controlled RCT of donepezil, but the participants did not have dementia
Saumier 2007	Open-label study, all participants on donepezil
Shua-Haim 2002a	Cross-sectional study of rivastigmine +donepezil compared with rivastigmine
Shua-Haim 2002b	Donepezil compared with rivastigmine compared with galantamine. No mention of randomisation
Stewart 1998	Open-label study, following participants in studies 301 and 302, during randomised phase and after, to examine costs of care
Tarraga 2006	This was a study of cognitive stimulation. All participants were taking a cholinesterase inhibitor
Teipel 2006	This was a cross-over study of donepezil, the primary outcome being cortical metabolic response assessed by PET. It was not a suitable design to assess cognition
Tessitore 2000	Open-label study, one group all on donepezil
Tettamanti 2000	Prospective observational study

(*Continued*)

Thal 2004	RCT, parallel groups, placebo, vitamin E and placebo. Participants with mild cognitive impairment, not AD
Thomas 2001	Donepezil compared with vitamin E
Touchon 2006	This was a subgroup analysis of a study that compared rivastigmine with donepezil. There was no placebo group
Tsolaki 2002	Donepezil compared with rivastigmine
Vanmechelen 2002	No mention of randomisation. Only AD biomarkers assessed
Wattmo 2008	Open-label, observational studies, all participants on donepezil
Weiner 2000	Open-label study, one group all on donepezil
Werber 2002	Non-randomised study of tacrine, donepezil or rivastigmine
Wilcock 2003	Single-blind, randomised, 52-week study comparing donepezil with galantamine. No placebo group
Winstein 2007	The duration of treatment in the RCT was only 4 weeks.
Wyeth 2005	Donepezil was compared with lecozatan. There was no placebo arm
Zhang 2012	Donepezil was compared with galantamine. There was no placebo arm

AD: Alzheimer's Disease; **EEG**: electro-encephalogram; **MMSE**: Mini-Mental State Exam; **MRI**: magnetic resonance imaging; **PET**: positron emission tomography; **RCT**: randomised controlled trial; **SPECT**: single-photon emission computed tomography

DATA AND ANALYSES

Comparison 1. Donepezil (10 mg/day) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-Cog (change from baseline at 24-26 weeks) ITT-LOCF	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 donepezil (10 mg/d) vs placebo at 24 weeks	5	1130	Mean Difference (IV, Fixed, 95% CI)	-2.67 [-3.31, -2.02]
2 MMSE (change from baseline at 24-26 weeks) ITT-LOCF	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 donepezil (10 mg/d) at 24 weeks	7	1757	Mean Difference (IV, Fixed, 95% CI)	1.05 [0.73, 1.37]
3 SIB (change from baseline at 24-26 weeks) ITT-LOCF	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 donepezil (10 mg/d) at 24 weeks	5	1348	Mean Difference (IV, Fixed, 95% CI)	5.92 [4.53, 7.31]
4 ADCS-ADL-severe (change from baseline at 24-26 weeks) ITT-LOCF	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 donepezil (10 mg/d) at 24 weeks	3	733	Mean Difference (IV, Fixed, 95% CI)	1.03 [0.21, 1.85]
5 CIBIC-Plus or CGIC (numbers improved at 24-26 weeks) ITT-LOCF	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 donepezil (10 mg/d) vs placebo at 24 weeks	6	1674	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.92 [1.54, 2.39]
6 CDR-SB (change from baseline at 24-26 weeks) ITT-LOCF	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 donepezil (10 mg/d) vs placebo at 24 weeks	3	1028	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.73, -0.33]
7 BEHAVE-AD (change from baseline at 24-26 weeks) ITT-LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 donepezil (10 mg/d) at 24 weeks	1	194	Mean Difference (IV, Fixed, 95% CI)	0.4 [-1.28, 2.08]
8 Behavioural disturbance (Total NPI) (change from baseline at 24-26 weeks) ITT-LOCF	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 donepezil (10 mg/d) at 24 weeks	4	1035	Mean Difference (IV, Fixed, 95% CI)	-1.62 [-3.43, 0.19]
9 QoL (participant-rated quality of life at 24-26 weeks) ITT-LOCF	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 donepezil (10 mg/d) vs placebo at 24 weeks	2	815	Mean Difference (IV, Fixed, 95% CI)	-2.79 [-8.15, 2.56]

10 Total number of withdrawals before end of treatment at 24-26 weeks	12		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 donepezil (10 mg/d) vs placebo at 24 weeks	12	2846	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [1.05, 1.50]
11 Total number of participants who suffered from at least one adverse event by 24-26 weeks	10		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 donepezil (10 mg/d) vs placebo at 24 weeks	10	2500	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [1.31, 1.95]

Comparison 2. Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-COG (change from baseline) completers	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 donepezil (5 mg/d) vs placebo at 12 weeks	6	1441	Mean Difference (IV, Fixed, 95% CI)	-2.15 [-2.69, -1.61]
1.2 donepezil (5 mg/d) vs placebo at 24 weeks	3	906	Mean Difference (IV, Fixed, 95% CI)	-2.02 [-2.77, -1.26]
1.3 donepezil (10 mg/d) vs placebo at 12 weeks	7	1245	Mean Difference (IV, Fixed, 95% CI)	-2.45 [-3.01, -1.89]
1.4 donepezil (10 mg/d) vs placebo at 24 weeks	5	848	Mean Difference (IV, Fixed, 95% CI)	-2.81 [-3.55, -2.06]
2 ADAS-COG (change from baseline) ITT-LOCF	13		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 donepezil (5 mg/d) vs placebo at 12 weeks	3	488	Mean Difference (IV, Fixed, 95% CI)	-2.27 [-3.16, -1.39]
2.2 donepezil (5 mg/d) vs placebo at 24 weeks	3	1089	Mean Difference (IV, Fixed, 95% CI)	-2.01 [-2.69, -1.34]
2.3 donepezil (10 mg/d) vs placebo at 12 weeks	5	459	Mean Difference (IV, Fixed, 95% CI)	-2.99 [-3.99, -1.99]
2.4 donepezil (10 mg/d) vs placebo at 24 weeks	5	1130	Mean Difference (IV, Fixed, 95% CI)	-2.67 [-3.31, -2.02]
3 MMSE (change from baseline) completers	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 donepezil (5 mg/d) vs placebo at 12 weeks	3	632	Mean Difference (IV, Fixed, 95% CI)	1.08 [0.61, 1.54]
3.2 donepezil (5 mg/d) vs placebo at 24 weeks	1	264	Mean Difference (IV, Fixed, 95% CI)	1.44 [0.64, 2.24]
3.3 donepezil (10 mg/d) vs placebo at 12 weeks	6	1173	Mean Difference (IV, Fixed, 95% CI)	1.26 [0.90, 1.62]
3.4 donepezil (10 mg/d) vs placebo at 24 weeks	6	1257	Mean Difference (IV, Fixed, 95% CI)	1.29 [0.90, 1.69]
3.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	189	Mean Difference (IV, Fixed, 95% CI)	1.84 [0.53, 3.15]

4 MMSE (change from baseline) ITT-LOCF	11		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 donepezil (5 mg/d) at 12 weeks	2	382	Mean Difference (IV, Fixed, 95% CI)	0.92 [0.32, 1.53]
4.2 donepezil (5 mg/d) at 24 weeks	2	358	Mean Difference (IV, Fixed, 95% CI)	1.22 [0.54, 1.90]
4.3 donepezil (10 mg/d) at 12 weeks	2	511	Mean Difference (IV, Fixed, 95% CI)	1.19 [0.61, 1.77]
4.4 donepezil (10 mg/d) at 24 weeks	7	1757	Mean Difference (IV, Fixed, 95% CI)	1.05 [0.73, 1.37]
4.5 donepezil (10 mg/d) at 52 weeks	1	272	Mean Difference (IV, Fixed, 95% CI)	1.70 [0.81, 2.59]
5 SIB (change from baseline) ITT-LOCF	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 donepezil (5 mg/d) at 24 weeks	1	198	Mean Difference (IV, Fixed, 95% CI)	6.7 [3.66, 9.74]
5.2 donepezil (10 mg/d) at 24 weeks	5	1348	Mean Difference (IV, Fixed, 95% CI)	5.92 [4.53, 7.31]
6 CIBIC-plus or CGIC (numbers improved) completers	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	228	Odds Ratio (M-H, Fixed, 95% CI)	3.93 [2.20, 7.02]
6.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	196	Odds Ratio (M-H, Fixed, 95% CI)	2.49 [1.40, 4.43]
7 CIBIC-plus or CGIC (numbers improved) ITT-LOCF	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [1.25, 3.53]
7.2 donepezil (5 mg/d) vs placebo at 24 weeks	4	1273	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.20 [1.69, 2.87]
7.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	302	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.70 [1.64, 4.46]
7.4 donepezil (10 mg/d) vs placebo at 24 weeks	6	1674	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.92 [1.54, 2.39]
8 CDR-SB (change from baseline) completers	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 donepezil (5 mg/d) vs placebo at 12 weeks	6	1461	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.38, -0.12]
8.2 donepezil (5 mg/d) vs placebo at 24 weeks	3	920	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-0.80, -0.36]
8.3 donepezil (10 mg/d) vs placebo at 12 weeks	5	1038	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.43, -0.12]
8.4 donepezil (10 mg/d) vs placebo at 24 weeks	2	656	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.83, -0.30]
9 CDR-SB (change from baseline) ITT-LOCF	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 donepezil (5 mg/d) vs placebo at 12 weeks	3	487	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.25, 0.21]
9.2 donepezil (5 mg/d) vs placebo at 24 weeks	3	1093	Mean Difference (IV, Fixed, 95% CI)	-0.51 [-0.70, -0.32]

9.3 donepezil (10 mg/d) vs placebo at 12 weeks	4	559	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.47, 0.00]
9.4 donepezil (10 mg/d) vs placebo at 24 weeks	3	1028	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.73, -0.33]
10 GBS or MENFIS - global assessment completers	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	228	Mean Difference (IV, Fixed, 95% CI)	-2.56 [-4.27, -0.85]
10.2 donepezil (10 mg/d) vs placebo at 12 weeks	1	258	Mean Difference (IV, Fixed, 95% CI)	-1.08 [-4.15, 1.99]
10.3 donepezil (10 mg/d) vs placebo at 24 weeks	1	243	Mean Difference (IV, Fixed, 95% CI)	-3.16 [-6.85, 0.53]
10.4 donepezil (10 mg/d) vs placebo at 52 weeks	1	190	Mean Difference (IV, Fixed, 95% CI)	-6.01 [-11.93, -0.09]
11 GBS - global assessment ITT-LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 donepezil (10 mg/d) vs placebo at 52 weeks	1	282	Mean Difference (IV, Fixed, 95% CI)	-3.26 [-7.38, 0.86]
12 ADL and IADL (CMCS) (change from baseline) completers	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 donepezil (5 mg/day) vs placebo at 24 weeks	1	228	Mean Difference (IV, Fixed, 95% CI)	-2.42 [-4.32, -0.52]
13 ADl and IADL (DAD) (change from baseline) completers	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 donepezil (10 mg/d) vs placebo at 12 weeks	1	254	Mean Difference (IV, Fixed, 95% CI)	4.83 [1.35, 8.31]
13.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	247	Mean Difference (IV, Fixed, 95% CI)	8.0 [3.61, 12.39]
14 ADCS-ADL-severe (change from baseline) ITT-LOCF	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 donepezil (5 mg/d) at 24 weeks	1	198	Mean Difference (IV, Fixed, 95% CI)	1.0 [-0.54, 2.54]
14.2 donepezil (10 mg/d) at 24 weeks	3	733	Mean Difference (IV, Fixed, 95% CI)	1.03 [0.21, 1.85]
15 PDS - progressive deterioration scale ITT-LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 donepezil (10 mg/d) vs placebo at 52 weeks	1	276	Mean Difference (IV, Fixed, 95% CI)	3.80 [1.70, 5.90]
16 Total number meeting criterion for functional decline before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
16.1 donepezil (10 mg/day) vs placebo	1	413	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.53 [0.36, 0.78]
17 Behavioural disturbance (total NPI) (change from baseline) completers	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 donepezil (10 mg/d) vs placebo at 12 weeks	2	279	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-4.43, 1.53]
17.2 donepezil (10 mg/d) vs placebo at 24 weeks	4	692	Mean Difference (IV, Fixed, 95% CI)	-1.04 [-3.16, 1.07]

18 BEHAVE-AD (change from baseline) ITT-LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 donepezil (5 mg/d) at 24 weeks	1	198	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.67, 1.67]
18.2 donepezil (10 mg/d) at 24 weeks	1	194	Mean Difference (IV, Fixed, 95% CI)	0.4 [-1.28, 2.08]
19 Behavioural disturbance (total NPI) (change from baseline) ITT-LOCF	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 donepezil (10 mg/d) at 24 weeks	4	1035	Mean Difference (IV, Fixed, 95% CI)	-1.62 [-3.43, 0.19]
20 QoL (participant-rated quality of life) completers	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 donepezil (5 mg/d) vs placebo at 12 weeks	4	1127	Mean Difference (IV, Fixed, 95% CI)	1.18 [-3.04, 5.40]
20.2 donepezil (5 mg/d) vs placebo at 24 weeks	2	681	Mean Difference (IV, Fixed, 95% CI)	2.26 [-3.64, 8.16]
20.3 donepezil (10 mg/d) vs placebo at 12 weeks	4	1031	Mean Difference (IV, Fixed, 95% CI)	1.16 [-3.20, 5.52]
20.4 donepezil (10 mg/d) vs placebo at 24 weeks	2	645	Mean Difference (IV, Fixed, 95% CI)	-1.17 [-7.26, 4.91]
21 QoL (participant-rated quality of life) ITT-LOCF	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 donepezil (5 mg/d) vs placebo at 12 weeks	2	377	Mean Difference (IV, Fixed, 95% CI)	3.07 [-3.81, 9.95]
21.2 donepezil (5 mg/d) vs placebo at 24 weeks	2	827	Mean Difference (IV, Fixed, 95% CI)	0.72 [-4.60, 6.04]
21.3 donepezil (10 mg/d) vs placebo at 12 weeks	2	318	Mean Difference (IV, Fixed, 95% CI)	-8.40 [-15.72, -1.08]
21.4 donepezil (10 mg/d) vs placebo at 24 weeks	2	815	Mean Difference (IV, Fixed, 95% CI)	-2.79 [-8.15, 2.56]
22 IADL (change from baseline) completers	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
22.1 donepezil (10 mg/d) vs placebo at 12 weeks	1	250	Mean Difference (IV, Fixed, 95% CI)	-4.31 [-7.72, -0.90]
22.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	243	Mean Difference (IV, Fixed, 95% CI)	-6.32 [-10.02, -2.62]
23 PSMS (change from baseline) completers	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
23.1 donepezil (10 mg/d) vs placebo at 12 weeks	1	255	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-1.17, 0.35]
23.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	244	Mean Difference (IV, Fixed, 95% CI)	-0.88 [-1.77, 0.01]
24 Time (mins/day) spent by carer assisting in IADL and PSMS (change from baseline) LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
24.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	221	Mean Difference (IV, Fixed, 95% CI)	-52.4 [-118.78, 13.98]
25 Total number who enter long-term institutional care before end of treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

25.1 donepezil (10 mg/d) at 52 weeks	1	286	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.10, 1.41]
26 Total number of withdrawals before end of treatment	21		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
26.1 donepezil (5 mg/d) vs placebo at 12 weeks	4	1079	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [1.22, 2.68]
26.2 donepezil (5 mg/d) vs placebo at 24 weeks	5	1386	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.66, 1.14]
26.3 donepezil (10 mg/d) vs placebo at 12 weeks	3	362	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.31 [1.21, 4.40]
26.4 donepezil (10 mg/d) vs placebo at 24 weeks	12	2846	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [1.05, 1.50]
26.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.62, 1.67]
27 Total number of participants who withdrew due to an adverse event	18		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
27.1 donepezil (5 mg/d) vs placebo at 12 weeks	3	513	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.33 [1.02, 5.28]
27.2 donepezil (5 mg/d) vs placebo at 24 weeks	4	1335	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.78 [0.52, 1.18]
27.3 donepezil (10 mg/d) vs placebo at 12 weeks	3	362	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.45 [1.40, 8.50]
27.4 donepezil (10 mg/d) vs placebo at 24 weeks	11	2819	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [1.33, 2.12]
27.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.45, 2.88]
28 Total number of participants who suffered from at least one adverse event	16		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
28.1 donepezil (5 mg/d) vs placebo at 12 weeks	3	513	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.70, 1.67]
28.2 donepezil (5 mg/d) vs placebo at 24 weeks	3	1018	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.40 [1.06, 1.86]
28.3 donepezil (10 mg/d) vs placebo at 12 weeks	2	323	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.55 [0.94, 2.55]
28.4 donepezil (10 mg/d) vs placebo at 24 weeks	10	2500	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [1.30, 1.94]
28.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.81, 2.51]
29 Total number of participants who suffered from abdominal pain	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
29.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.53, 4.17]
29.2 donepezil (5 mg/d) vs placebo at 24 weeks	1	267	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.11, 3.75]
29.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.31, 3.06]
29.4 donepezil (10 mg/d) vs placebo at 24 weeks	3	627	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.58, 2.24]

29.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.40 [0.12, 1.32]
30 Total number of participants who suffered from abnormal gait	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
30.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [0.63, 3.98]
31 Total number of participants who suffered from abnormal dreams	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 donepezil (10 mg/d) at 24 weeks	1	153	Odds Ratio (M-H, Fixed, 95% CI)	12.49 [0.71, 218.72]
32 Total number of participants who suffered from accidental fall	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
32.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.40, 3.76]
32.2 donepezil (10 mg/d) vs placebo at 24 weeks	2	449	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.58, 2.02]
33 Total number of participants who suffered from accidental injury	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
33.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.32, 1.94]
33.2 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.36, 2.11]
33.3 donepezil (10 mg/d) vs placebo at 24 weeks	4	899	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.87, 1.98]
34 Total number of participants who suffered from agitation	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
34.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.23, 1.57]
34.2 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.36, 2.11]
34.3 donepezil (10 mg/d) vs placebo at 24 weeks	2	551	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.60, 2.22]
35 Total number of participants who suffered from anorexia	9		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
35.1 donepezil (5 mg/d) vs placebo at 12 weeks	2	433	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.91 [0.61, 6.02]
35.2 donepezil (5 mg/d) vs placebo at 24 weeks	4	1334	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.90 [0.88, 4.13]
35.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.37 [0.81, 6.90]
35.4 donepezil (10 mg/d) vs placebo at 24 weeks	6	1931	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.01 [1.96, 4.62]
36 Total number of participants who suffered from anxiety	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
36.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.28, 1.92]

36.2 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.84, 4.60]
37 Total number of participants who suffered from arthralgia	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
37.1 donepezil (10 mg/d) vs placebo at 24 weeks	2	498	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.62, 2.40]
38 Total number of participants who suffered from asthenia	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
38.1 donepezil (10 mg/d) vs placebo at 24 weeks	4	899	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.58 [0.95, 2.64]
38.2 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.24 [0.82, 6.13]
39 Total number of participants who suffered from back pain	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
39.1 donepezil (10 mg/d) vs placebo at 24 weeks	2	498	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [0.87, 3.23]
40 Total number of participants who suffered from cold syndrome	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
40.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.30, 1.99]
40.2 donepezil (5 mg/d) vs placebo at 24 weeks	2	473	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [0.86, 2.88]
40.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.25, 1.77]
40.4 donepezil (10 mg/d) vs placebo at 24 weeks	1	201	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.54, 2.29]
41 Total number of participants who suffered from confusion	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
41.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	544	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.61, 2.40]
41.2 donepezil (10 mg/d) vs placebo at 24 weeks	3	1045	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.57, 1.56]
41.3 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.15, 1.38]
42 Total number of participants who suffered from conjunctivitis	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
42.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.93 [0.72, 5.20]
43 Total number of participants who suffered from constipation	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
43.1 donepezil (5 mg/d) vs placebo at 24 weeks	2	473	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.06 [0.73, 5.80]
43.2 donepezil (10 mg/d) vs placebo at 24 weeks	2	449	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.41, 2.46]
43.3 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.24, 1.88]
44 Total number of participants who suffered from contusion	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

44.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [0.41, 7.61]
44.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	201	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.22, 5.57]
45 Total number of participants who suffered from cystitis	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
45.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.50, 4.63]
46 Total number of participants who suffered from depression	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
46.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [0.54, 4.99]
46.2 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.69, 3.37]
47 Total number of participants who suffered from diarrhoea	13		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
47.1 donepezil (5 mg/d) vs placebo at 12 weeks	2	390	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.64 [1.05, 6.63]
47.2 donepezil (5 mg/d) vs placebo at 24 weeks	4	1334	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [1.19, 2.89]
47.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.22 [1.87, 9.54]
47.4 donepezil (10 mg/d) vs placebo at 24 weeks	9	2622	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.69 [2.05, 3.55]
47.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.41, 2.52]
48 Total number of participants who suffered from dizziness	10		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
48.1 donepezil (5 mg/d) vs placebo at 12 weeks	3	512	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.55, 2.31]
48.2 donepezil (5 mg/d) vs placebo at 24 weeks	2	861	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [0.82, 2.63]
48.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.60, 3.18]
48.4 donepezil (10 mg/d) vs placebo at 24 weeks	6	1830	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [1.19, 2.63]
48.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.55 [0.55, 4.36]
49 Total number of participants who suffered from ecchymosis	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
49.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [0.55, 4.47]
50 Total number of participants who suffered from eczema	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
50.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	267	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.23 [0.75, 70.12]
51 Total number of participants who suffered from fatigue	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
51.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.20, 1.83]

51.2 donepezil (5 mg/d) vs placebo at 24 weeks	1	316	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.70 [0.81, 8.97]
51.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.60, 3.66]
51.4 donepezil (10 mg/d) vs placebo at 24 weeks	1	319	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.63 [1.29, 10.21]
52 Total number of participants who suffered from fever	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
52.1 donepezil (5 mg/d) vs placebo at 24 weeks	2	473	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.53, 7.32]
52.2 donepezil (10 mg/d) vs placebo at 24 weeks	2	409	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.58, 2.41]
53 Total number of participants who suffered from fracture	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
53.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	267	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.05, 2.51]
53.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [0.49, 5.52]
53.3 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [0.54, 4.99]
54 Total number of participants who suffered from gastroenteritis	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
54.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.24, 1.51]
55 Total number of participants who suffered from haemorrhage	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
55.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.35, 3.01]
56 Total number of participants who suffered from hallucinations	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
56.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.68 [1.24, 17.66]
57 Total number of participants who suffered from headache	9		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
57.1 donepezil (5 mg/d) vs placebo at 12 weeks	3	512	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.39 [0.71, 2.71]
57.2 donepezil (5 mg/d) vs placebo at 24 weeks	2	812	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.66, 1.75]
57.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.71, 3.04]
57.4 donepezil (10 mg/d) vs placebo at 24 weeks	4	1174	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.88, 1.82]
57.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.51, 3.12]
58 Total number of participants who suffered from hostility	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
58.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.58, 2.99]

58.2 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.16, 1.61]
59 Total number of participants who suffered from loss of appetite	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
59.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Odds Ratio (M-H, Fixed, 95% CI)	2.68 [0.51, 14.15]
59.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	201	Odds Ratio (M-H, Fixed, 95% CI)	2.24 [0.40, 12.51]
60 Total number of participants who suffered from infection	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
60.1 donepezil (10 mg/d) vs placebo at 24 weeks	2	551	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.39 [0.76, 2.55]
61 Total number of participants who suffered from inflammation of upper airway	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
61.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	267	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.25, 8.46]
62 Total number of participants who suffered from insomnia	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
62.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [0.67, 3.92]
62.2 donepezil (5 mg/d) vs placebo at 24 weeks	1	544	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [0.85, 3.69]
62.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [1.69, 6.76]
62.4 donepezil (10 mg/d) vs placebo at 24 weeks	3	1043	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.40 [1.38, 4.15]
62.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.63, 3.36]
63 Total number of participants who suffered from increased cough	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
63.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.08, 1.00]
63.2 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.11, 1.26]
63.3 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.56, 2.51]
64 Total number of participants who suffered from myasthenia	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
64.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [0.54, 7.74]
65 Total number of participants who suffered from muscle cramp	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
65.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.53, 4.17]
65.2 donepezil (5 mg/d) vs placebo at 24 weeks	1	316	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.48 [1.56, 19.27]

65.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.76, 5.06]
65.4 donepezil (10 mg/d) vs placebo at 24 weeks	1	319	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.00 [1.98, 18.18]
66 Total number of participants who suffered from nausea	13		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
66.1 donepezil (5 mg/d) vs placebo at 12 weeks	3	513	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.70, 2.71]
66.2 donepezil (5 mg/d) vs placebo at 24 weeks	3	1128	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.74, 2.15]
66.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.95 [1.58, 5.51]
66.4 donepezil (10 mg/d) vs placebo at 24 weeks	8	2184	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.06 [2.26, 4.14]
66.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.59, 2.75]
67 Total number of participants who suffered from pain	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
67.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.56, 2.85]
67.2 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.93 [0.93, 4.01]
67.3 donepezil (10 mg/d) vs placebo at 24 weeks	2	551	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.64, 2.01]
68 Total number of participants who suffered from peripheral oedema	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
68.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.20 [0.05, 0.74]
68.2 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.15, 1.53]
68.3 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [1.02, 4.09]
69 Total number of participants who suffered from pneumonia	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
69.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [0.65, 4.19]
70 Total number of participants who suffered from rash	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
70.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.37, 1.41]
71 Total number of participants who suffered from restlessness	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
71.1 donepezil (5 mg/d) vs placebo at 24 weeks	2	473	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.44, 5.37]
71.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	201	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.15 [0.22, 20.95]
72 Total number of participants who suffered from respiratory tract infection	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

72.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.45, 3.83]
72.2 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.29, 2.20]
72.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.24, 2.67]
72.4 donepezil (10 mg/d) vs placebo at 24 weeks	2	491	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.50, 1.65]
73 Total number of participants who suffered from rhinitis	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
73.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.45, 3.83]
73.2 donepezil (5 mg/d) vs placebo at 24 weeks	1	316	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.31 [0.05, 1.82]
73.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.24, 2.67]
73.4 donepezil (10 mg/d) vs placebo at 24 weeks	2	527	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.75, 2.56]
74 Total number of participants who suffered from vomiting	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
74.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.22, 2.18]
74.2 donepezil (5 mg/d) vs placebo at 24 weeks	4	1334	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.68, 2.17]
74.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.40 [0.53, 3.72]
74.4 donepezil (10 mg/d) vs placebo at 24 weeks	6	1908	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.65 [1.90, 3.70]
75 Total number of participants who suffered from skin ulcer	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
75.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.56, 4.03]
76 Total number of participants who suffered from syncope	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
76.1 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.27 [0.75, 6.88]
77 Total number of participants who suffered from tremor	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
77.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	208	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.58 [1.01, 12.71]
78 Total number of participants who suffered from urinary incontinence	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
78.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	343	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.31 [0.79, 6.72]
79 Total number of participants who suffered from urinary tract infection	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
79.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.47 [0.22, 0.99]

79.2 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.13, 0.67]
79.3 donepezil (10 mg/d) vs placebo at 24 weeks	5	1188	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.59, 1.31]
79.4 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.31, 2.08]
80 Total number of participants who suffered from vertigo	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
80.1 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.36 [1.15, 9.82]
81 Total number of participants who suffered from weight loss	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
81.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.19, 4.89]
81.2 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.48 [0.74, 8.23]
81.3 donepezil (10 mg/d) vs placebo at 24 weeks	3	811	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.90 [1.08, 3.35]
82 total number of deaths before end of treatment	17		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
82.1 donepezil (5 mg/d) vs placebo at 12 weeks	3	513	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.06, 15.29]
82.2 donepezil (5 mg/d) vs placebo at 24 weeks	4	1334	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.25, 4.10]
82.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.60]
82.4 donepezil (10 mg/d) vs placebo at 24 weeks	12	2847	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.46, 1.19]
82.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.36 [0.30, 6.07]
83 Total number of participants who suffered from at least one serious adverse event	11		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
83.1 donepezil (5 mg/d) vs placebo at 12 weeks	1	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.27, 2.51]
83.2 donepezil (5 mg/d) vs placebo at 24 weeks	3	1067	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.49, 1.18]
83.3 donepezil (10 mg/d) vs placebo at 12 weeks	1	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.27, 2.50]
83.4 donepezil (10 mg/d) vs placebo at 24 weeks	9	2599	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.71, 1.14]
83.5 donepezil (10 mg/d) vs placebo at 52 weeks	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.99 [1.11, 3.59]

Comparison 3. Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient and carer health resource utilisation over 24 weeks (Australia, Canada, France)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 In-home nursing visits	1	289	Mean Difference (IV, Fixed, 95% CI)	0.50 [-2.61, 3.61]
1.2 Other healthcare professional visits	1	289	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-2.98, 0.58]
1.3 Day hospital visits	1	289	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.70, 0.70]
1.4 AD-related physician visits	1	289	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.71, 0.51]
1.5 AD-related medication	1	289	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.53, 0.33]
1.6 Residential care days	1	289	Mean Difference (IV, Fixed, 95% CI)	-6.9 [-17.12, 3.32]
1.7 Respite care days	1	289	Mean Difference (IV, Fixed, 95% CI)	0.9 [-0.36, 2.16]
1.8 Day centre visits	1	289	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-4.90, 3.90]
1.9 In-home nursing visits	1	289	Mean Difference (IV, Fixed, 95% CI)	0.50 [-2.61, 3.61]
1.10 Home help visits	1	289	Mean Difference (IV, Fixed, 95% CI)	2.5 [-9.73, 14.73]
1.11 Meal delivery	1	289	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-12.46, 6.66]
1.12 Carer - counselling visits	1	289	Mean Difference (IV, Fixed, 95% CI)	0.4 [-0.28, 1.08]
1.13 Carer-related physician visits	1	289	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.21, 1.41]
1.14 Unpaid carer time (total hours)	1	289	Mean Difference (IV, Fixed, 95% CI)	-34.0 [-191.45, 123.45]
2 Health resource cost/participant (CAD) over 24 weeks in 1998 (Australia, Canada, France)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 In-home nursing care	1	289	Mean Difference (IV, Fixed, 95% CI)	22.00 [-118.50, 162.50]
2.2 Other healthcare professional services	1	289	Mean Difference (IV, Fixed, 95% CI)	-103.00 [-243.15, 37.15]
2.3 Day hospital use	1	289	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-74.71, 72.71]
2.4 AD-related physician services	1	289	Mean Difference (IV, Fixed, 95% CI)	-15.0 [-42.21, 12.21]
2.5 AD-related medication	1	289	Mean Difference (IV, Fixed, 95% CI)	25.0 [-5.59, 55.59]
2.6 Acute-care hospital stays	1	289	Mean Difference (IV, Fixed, 95% CI)	22.00 [-118.50, 162.50]
2.7 In-home nursing care	1	289	Mean Difference (IV, Fixed, 95% CI)	-22.00 [-206.26, 162.26]
2.8 Residential care	1	289	Mean Difference (IV, Fixed, 95% CI)	-595.0 [-1604.31, 414.31]
2.9 Respite care	1	289	Mean Difference (IV, Fixed, 95% CI)	86.0 [-37.07, 209.07]
2.10 Day centre	1	289	Mean Difference (IV, Fixed, 95% CI)	-34.0 [-311.05, 243.05]
2.11 Home help	1	289	Mean Difference (IV, Fixed, 95% CI)	112.0 [-524.20, 748.20]
2.12 Meal delivery service	1	289	Mean Difference (IV, Fixed, 95% CI)	-41.0 [-169.68, 87.68]

2.13 Total cost including cost of donepezil	1	289	Mean Difference (IV, Fixed, 95% CI)	34.0 [-641.33, 709.33]
3 Health resource cost/carer (CAD) over 24 weeks in 1998 (Australia, Canada, France)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Counseling	1	289	Mean Difference (IV, Fixed, 95% CI)	25.00 [-26.81, 76.81]
3.2 Physician visits	1	289	Mean Difference (IV, Fixed, 95% CI)	15.0 [-6.05, 36.05]
3.3 Medication	1	289	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-27.26, 11.26]
3.4 Total carer costs	1	289	Mean Difference (IV, Fixed, 95% CI)	31.0 [7.22, 54.78]
4 Unpaid carer time cost (CAD) in 1998 (Australia, Canada, France)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 Total cost to society (CAD) in 1998 (Australia, Canada, France)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6 Health resource cost/participant (USD) over one year in 1999 (northern Europe)	1		MD (Fixed, 95% CI)	Subtotals only
6.1 Total participant direct costs including cost of donepezil	1	286	MD (Fixed, 95% CI)	291.0 [-2645.03, 3227.03]
7 Health resource cost/carer (USD) over one year in 1999 (northern Europe)	1		MD (Fixed, 95% CI)	Subtotals only
7.1 Total carer direct medical costs	1	286	MD (Fixed, 95% CI)	355.0 [-84.03, 794.03]
7.2 Total carer time costs	1	286	MD (Fixed, 95% CI)	1033.0 [-1765.83, 3831.83]
8 Health resource cost/participant + carer (USD) over one year in 1999 (northern Europe)	1		MD (Fixed, 95% CI)	Subtotals only
8.1 Total participant and carer costs including cost of donepezil	1	286	MD (Fixed, 95% CI)	1097.0 [-3052.24, 5246.24]

Comparison 4. Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SIB (change from baseline) at 24 weeks ITT-LOCF	2	1704	Mean Difference (IV, Fixed, 95% CI)	1.05 [-0.15, 2.25]
2 MMSE (change from baseline at 24 weeks) ITT-LOCF	1	1370	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.33, 0.73]
3 ADCS-ADL-sev (change from baseline) at 24 weeks ITT-LOCF	1	1369	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.18, 1.18]

4 CIBIC-plus (numbers improved) by end of treatment at 24 weeks	2	1704	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.78, 1.26]
5 total number of patients who withdrew before end of treatment at 24 weeks	2	1818	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [1.59, 2.57]
6 total number of patients who withdrew due to an adverse event before end of treatment at 24 weeks	2	1818	Odds Ratio (M-H, Fixed, 95% CI)	2.51 [1.83, 3.45]
7 total number of patients who suffered an adverse event before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [1.34, 2.03]
8 total number of patients who suffered a serious adverse event before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.71, 1.38]
9 total number of patients who suffered an adverse event of asthenia before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	3.31 [0.98, 11.19]
10 total number of patients who suffered an adverse event of contusion before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	4.99 [1.88, 13.26]
11 total number of patients who suffered an adverse event of anorexia before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	3.24 [1.52, 6.88]
12 total number of patients who suffered an adverse event of diarrhoea before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [1.15, 2.68]
13 total number of patients who suffered an adverse event of dizziness before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.82, 2.60]
14 total number of patients who suffered an adverse event of fatigue before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	2.86 [0.98, 8.31]
15 total number of patients who suffered an adverse event of headache before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.74, 2.47]
16 total number of patients who suffered an adverse event of insomnia before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.67, 2.26]
17 total number of patients who suffered an adverse event of nausea before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	3.36 [2.09, 5.42]

18 total number of patients who suffered an adverse event of vomiting before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	3.88 [2.27, 6.65]
19 total number of patients who suffered an adverse event of weight decrease before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [1.12, 3.70]
20 total number of patients who suffered an adverse event of accidental fall before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.60, 1.88]
21 total number of patients who suffered an adverse event of urinary tract infection before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.62, 1.89]
22 total number of patients who suffered an adverse event of bradycardia and sinus bradycardia before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	4.5 [1.36, 14.91]
23 total number of patients who suffered an adverse event of agitation before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.58, 1.83]
24 total number of patients who suffered an adverse event of aggression before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.53, 2.12]
25 total number of patients who suffered an adverse event of urinary incontinence before end of treatment at 24 weeks	1	1434	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [0.80, 4.88]
26 total number of patients who suffered an adverse event of somnolence before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	2.43 [0.97, 6.12]
27 total number of patients who died before end of treatment at 24 weeks	2	1785	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.24, 1.95]
28 total number of patients who suffered an adverse event of nasopharyngitis before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.83, 3.62]
29 total number of patients who suffered an adverse event of decreased appetite before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	2.45 [1.00, 6.02]
30 total number of patients who suffered an adverse event of ECG QT prolonged before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.39, 4.07]

31 total number of patients who suffered an adverse event of anger before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.67, 4.41]
32 total number of patients who suffered an adverse event of constipation before end of treatment at 24 weeks end of treatment	1	351	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.22, 1.95]
33 total number of patients who suffered an adverse event of bronchitis before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	2.28 [0.44, 11.90]
34 total number of patients who suffered an adverse event of conjunctivitis before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	10.15 [0.56, 184.91]
35 total number of patients who suffered an adverse event of upper respiratory tract infection before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.26, 5.45]
36 total number of patients who suffered an adverse event of arthralgia before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	3.65 [0.40, 32.96]
37 total number of patients who suffered an adverse event of back pain before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.33, 10.02]
38 total number of patients who suffered an adverse event of spinal compression fracture before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	8.26 [0.44, 154.51]
39 total number of patients who suffered an adverse event of dermatitis contact before end of treatment at 24 weeks	1	351	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.08, 2.45]

Comparison 5. Donepezil (15-20 mg/day) versus donepezil (10 mg/day)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number who suffered an adverse event before end of treatment at 26 weeks	1	31	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.36, 7.60]

Comparison 6. Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMAI (change from baseline) completers	1	221	Mean Difference (Fixed, 95% CI)	0.18 [-4.23, 4.59]
2 NPI (change from baseline) completers	1	201	Mean Difference (Fixed, 95% CI)	0.1 [-3.78, 3.98]
3 NPI caregiver distress (change from baseline)	1	200	Mean Difference (Fixed, 95% CI)	-0.45 [-2.06, 1.16]
4 Total number of withdrawals before end of treatment	1	259	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.31, 1.41]
5 Total number of participants who suffered from nausea	1	259	Odds Ratio (M-H, Fixed, 95% CI)	3.12 [0.32, 30.40]
6 Total number of participants who suffered from diarrhoea	1	259	Odds Ratio (M-H, Fixed, 95% CI)	5.20 [0.25, 109.33]
7 Total number of participants who suffered from rash	1	259	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.18, 23.04]
8 Total number of participants who suffered from increased agitation	1	259	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.11, 4.12]
9 Total number of participants who suffered from postural hypotension	1	259	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.39]
10 Total number of participants who suffered from a fall	1	259	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.14, 7.38]
11 Total number of participants who suffered from femoral fracture	1	259	Odds Ratio (M-H, Fixed, 95% CI)	5.20 [0.25, 109.33]
12 Total number of participants who suffered from a stroke	1	259	Odds Ratio (M-H, Fixed, 95% CI)	3.09 [0.12, 76.66]
13 Total number of participants who suffered from myocardial infarct	1	259	Odds Ratio (M-H, Fixed, 95% CI)	3.09 [0.12, 76.66]
14 Total number of participants who suffered from urinary tract infection	1	259	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.11, 4.12]
15 Total number of participants who suffered from chest infection	1	259	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.54]
16 Total number of participants who suffered from seizure	1	259	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.11, 4.12]
17 Total number of deaths	1	259	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.17, 3.47]

Comparison 7. Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADAS-Cog (change from baseline at 24 weeks) ITT-LOCF	2	818	Mean Difference (IV, Fixed, 95% CI)	-1.05 [-1.80, -0.30]
2 MMSE (change from baseline at 24 weeks) ITT-LOCF	1	303	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.55, 0.85]
3 SIB (change from baseline) at 24 weeks ITT-LOCF	1	188	Mean Difference (IV, Fixed, 95% CI)	2.2 [-1.00, 5.40]
4 ADCS-ADL-sev (change from baseline) at 24 weeks ITT-LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 CIBIC-plus (numbers improved) by end of treatment at 26 weeks	3	981	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.94, 1.67]
6 CDR-SB (change from baseline at 24 weeks) ITT-LOCF	2	824	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.29, 0.14]
7 BEHAVE-AD (change from baseline) at 24 weeks ITT-LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8 QoL (change from baseline at 24 weeks) ITT-LOCF	1	302	Mean Difference (IV, Fixed, 95% CI)	-8.33 [-16.23, -0.43]
9 Total number of participants who withdrew before end of treatment at 26 weeks	3	1052	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [1.24, 2.23]
10 Total number of participants who withdrew due to an adverse event before end of treatment at 26 weeks	3	1052	Odds Ratio (M-H, Fixed, 95% CI)	2.41 [1.63, 3.57]
11 Total number of participants who suffered an adverse event before end of treatment at 26 weeks	2	741	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [1.07, 2.28]
12 Total number of participants who suffered an adverse event of anorexia before end of treatment at 26 weeks	3	1052	Odds Ratio (M-H, Fixed, 95% CI)	2.72 [1.48, 5.00]
13 Total number of participants who suffered an adverse event of confusion before end of treatment at 26 weeks	1	545	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.41, 1.64]
14 Total number of participants who suffered an adverse event of diarrhoea before end of treatment at 26 weeks	3	1052	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [1.22, 2.61]
15 Total number of participants who suffered an adverse event of dizziness before end of treatment at 26 weeks	2	855	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.83, 2.28]

16 Total number of participants who suffered an adverse event of fatigue before end of treatment at 26 weeks	1	311	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.60, 3.80]
17 Total number of participants who suffered an adverse event of headache before end of treatment at 26 weeks	1	545	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.73, 1.97]
18 Total number of participants who suffered an adverse event of insomnia before end of treatment at 26 weeks	1	545	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.61, 2.19]
19 Total number of participants who suffered an adverse event of muscle cramp before end of treatment at 26 weeks	1	311	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.55, 3.26]
20 Total number of participants who suffered an adverse event of nausea before end of treatment at 26 weeks	2	855	Odds Ratio (M-H, Fixed, 95% CI)	4.22 [2.67, 6.70]
21 Total number of participants who suffered an adverse event of rhinitis before end of treatment at 26 weeks	1	311	Odds Ratio (M-H, Fixed, 95% CI)	9.30 [1.16, 74.35]
22 Total number of participants who suffered an adverse event of vomiting before end of treatment at 26 weeks	3	1052	Odds Ratio (M-H, Fixed, 95% CI)	3.40 [2.10, 5.48]
23 Total number of participants who suffered an adverse event of cold syndrome before end of treatment at 26 weeks	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.49, 2.04]
24 Total number of participants who suffered an adverse event of accidental fall before end of treatment at 26 weeks	1	197	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.29, 2.77]
25 Total number of participants who suffered an adverse event of respiratory tract infection before end of treatment at 26 weeks	1	197	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.29, 2.77]
26 Total number of participants who suffered an adverse event of constipation before end of treatment at 26 weeks	1	197	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.20, 2.03]
27 Total number of participants who suffered an adverse event of fever before end of treatment at 26 weeks	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [0.42, 7.72]

28 Total number of participants who suffered an adverse event of loss of appetite before end of treatment at 26 weeks	1	197	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.22, 3.21]
29 Total number of participants who suffered an adverse event of bruising before end of treatment at 26 weeks	1	197	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.14, 2.67]
30 Total number of participants who suffered an adverse event of restlessness before end of treatment at 26 weeks	1	197	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.07, 1.71]

Comparison 8. Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MMSE (change from baseline) ITT-LOCF	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 donepezil (10 mg/d) at 24 weeks	4	1102	Mean Difference (IV, Fixed, 95% CI)	0.97 [0.56, 1.38]
2 SIB (change from baseline) ITT-LOCF	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 donepezil (5 mg/d) at 24 weeks	1	198	Mean Difference (IV, Fixed, 95% CI)	6.7 [3.66, 9.74]
2.2 donepezil (10 mg/d) at 24 weeks	5	1348	Mean Difference (IV, Fixed, 95% CI)	5.92 [4.53, 7.31]
3 CIBIC-Plus or CGIC (numbers improved) ITT-LOCF	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	198	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.54 [0.83, 2.87]
3.2 donepezil (10 mg/d) vs placebo at 24 weeks	3	755	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.78 [1.31, 2.43]
4 ADCS-ADL-severe (change from baseline) ITT-LOCF	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 donepezil (5 mg/d) at 24 weeks	1	198	Mean Difference (IV, Fixed, 95% CI)	1.0 [-0.54, 2.54]
4.2 donepezil (10 mg/d) at 24 weeks	3	733	Mean Difference (IV, Fixed, 95% CI)	1.03 [0.21, 1.85]
5 BEHAVE-AD (change from baseline) ITT-LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 donepezil (5 mg/d) at 24 weeks	1	198	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.67, 1.67]
5.2 donepezil (10 mg/d) at 24 weeks	1	194	Mean Difference (IV, Fixed, 95% CI)	0.4 [-1.28, 2.08]
6 Behavioural disturbance (total NPI) (change from baseline) ITT-LOCF	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

6.1 donepezil (10 mg/d) at 24 weeks	3	827	Mean Difference (IV, Fixed, 95% CI)	-2.18 [-4.11, -0.25]
7 Time (mins/day) spent by carer assisting in IADL and PSMS (change from baseline) LOCF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	221	Mean Difference (IV, Fixed, 95% CI)	-52.4 [-118.78, 13.98]
8 Total number of withdrawals before end of treatment	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.32, 1.43]
8.2 donepezil (10 mg/d) vs placebo at 24 weeks	5	1396	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [1.02, 1.71]
9 Total number of participants who withdrew due to an adverse event	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.29, 1.89]
9.2 donepezil (10 mg/d) vs placebo at 24 weeks	5	1396	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [1.23, 2.42]
10 Total number of participants who suffered from at least one adverse event	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.69, 2.46]
10.2 donepezil (10 mg/d) vs placebo at 24 weeks	5	1396	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [1.23, 2.05]
11 Total number of participants who suffered from abdominal pain	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
11.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.36, 2.30]
12 Total number of participants who suffered from accidental fall	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
12.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.40, 3.76]
12.2 donepezil (10 mg/d) vs placebo at 24 weeks	2	449	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.58, 2.02]
13 Total number of participants who suffered from accidental injury	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
13.1 donepezil (10 mg/d) vs placebo at 24 weeks	2	538	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.46, 1.70]
14 Total number of participants who suffered from anorexia	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
14.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.53 [0.05, 5.16]
14.2 donepezil (10 mg/d) vs placebo at 24 weeks	3	857	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.32 [1.20, 4.48]

15 Total number of participants who suffered from anxiety	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
15.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.28, 1.92]
16 Total number of participants who suffered from arthralgia	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
16.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.06 [1.28, 12.86]
17 Total number of participants who suffered from asthenia	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
17.1 donepezil (10 mg/d) vs placebo at 24 weeks	2	538	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.59, 2.50]
18 Total number of participants who suffered from back pain	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
18.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [0.63, 4.22]
19 Total number of participants who suffered from cold syndrome	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
19.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.55, 2.28]
19.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	201	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.54, 2.29]
20 Total number of participants who suffered from confusion	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
20.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.43, 3.06]
21 Total number of participants who suffered from constipation	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
21.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.11 [0.66, 6.75]
21.2 donepezil (10 mg/d) vs placebo at 24 weeks	2	449	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.41, 2.46]
22 Total number of participants who suffered from contusion	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [0.41, 7.61]
22.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	201	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.22, 5.57]
23 Total number of participants who suffered from cystitis	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
23.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.50, 4.63]
24 Total number of participants who suffered from depression	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
24.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [0.54, 4.99]
25 Total number of participants who suffered from diarrhoea	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
25.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.58 [0.45, 5.62]

25.2 donepezil (10 mg/d) vs placebo at 24 weeks	5	1395	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.57 [1.65, 4.01]
26 Total number of participants who suffered from dizziness	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
26.1 donepezil (10 mg/d) vs placebo at 24 weeks	2	603	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [0.69, 3.66]
27 Total number of participants who suffered from fever	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
27.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.87 [0.40, 20.69]
27.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	201	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.32 [0.85, 21.86]
28 Total number of participants who suffered from fracture	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
28.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [0.49, 5.52]
29 Total number of participants who suffered from gastroenteritis	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
29.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.24, 1.51]
30 Total number of participants who suffered from hallucinations	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
30.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.68 [1.24, 17.66]
31 Total number of participants who suffered from pneumonia	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
31.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [0.65, 4.19]
32 Total number of participants who suffered from hostility	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
32.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.58, 2.99]
33 Total number of participants who suffered from insomnia	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
33.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	343	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.70 [0.99, 7.35]
34 Total number of participants who suffered from loss of appetite	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
34.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Odds Ratio (M-H, Fixed, 95% CI)	2.68 [0.51, 14.15]
34.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	201	Odds Ratio (M-H, Fixed, 95% CI)	2.24 [0.40, 12.51]
35 Total number of participants who suffered from nausea	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
35.1 donepezil (10 mg/d) vs placebo at 24 weeks	3	828	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.11 [1.16, 3.85]
36 Total number of participants who suffered from restlessness	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

36.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.54 [1.01, 20.41]
36.2 donepezil (10 mg/d) vs placebo at 24 weeks	1	201	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.15 [0.22, 20.95]
37 Total number of participants who suffered from headache	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
37.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.86 [1.22, 6.69]
38 Total number of participants who suffered from respiratory tract infection	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
38.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.29, 2.20]
38.2 donepezil (10 mg/d) vs placebo at 24 weeks	2	491	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.50, 1.65]
39 Total number of participants who suffered from vomiting	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
39.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.35, 3.08]
39.2 donepezil (10 mg/d) vs placebo at 24 weeks	3	834	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.42 [1.37, 4.31]
40 Total number of participants who suffered from urinary incontinence	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
40.1 donepezil (10 mg/d) vs placebo at 24 weeks	1	343	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.31 [0.79, 6.72]
41 Total number of participants who suffered from urinary tract infection	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
41.1 donepezil (10 mg/d) vs placebo at 24 weeks	3	851	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.55, 1.48]
42 Total number of participants who suffered from weight loss	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
42.1 donepezil (10 mg/d) vs placebo at 24 weeks	2	603	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [0.69, 3.66]
43 Total number of deaths before end of treatment	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
43.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [0.21, 19.83]
43.2 donepezil (10 mg/d) vs placebo at 24 weeks	5	1396	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.41, 1.25]
44 Total number of participants who suffered from at least one serious adverse event	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
44.1 donepezil (5 mg/d) vs placebo at 24 weeks	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.36, 1.82]
44.2 donepezil (10 mg/d) vs placebo at 24 weeks	5	1396	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.59, 1.08]

Analysis 1.1. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 1 ADAS-Cog (change from baseline at 24-26 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 1 ADAS-Cog (change from baseline at 24-26 weeks) ITT-LOCF

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks							
Burns 1999	254	-1.26 (5.5)	264	1.66 (5.5)		46.0 %	-2.92 [-3.87, -1.97]
Maher-Edwards 2011	67	-1.5 (6)	61	-0.3 (6.26)		9.1 %	-1.20 [-3.33, 0.93]
Moraes 2006b	17	-7.3 (18.4)	18	3.8 (26.3)		0.2 %	-11.10 [-26.07, 3.87]
Rogers 1998b	150	-1.06 (5.43)	153	1.82 (5.43)		27.6 %	-2.88 [-4.10, -1.66]
Seltzer 2004	91	-1.64 (4.69)	55	0.69 (4.61)		17.1 %	-2.33 [-3.88, -0.78]
Subtotal (95% CI)	**579**		**551**			**100.0 %**	**-2.67 [-3.31, -2.02]**
Heterogeneity: Chi^2 = 3.61, df = 4 (P = 0.46); I^2 =0.0%							
Test for overall effect: Z = 8.13 (P < 0.00001)							

Analysis 1.2. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 2 MMSE (change from baseline at 24-26 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 2 MMSE (change from baseline at 24-26 weeks) ITT-LOCF

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (10 mg/d) at 24 weeks							
Black 2007	150	0.65 (3.31)	141	-0.03 (3.32)		17.7 %	0.68 [-0.08, 1.44]
Feldman 2001	131	1.35 (4.01)	139	-0.44 (3.99)		11.3 %	1.79 [0.84, 2.74]
Jia 2017	150	1.7 (3.3)	151	1 (3.44)		17.7 %	0.70 [-0.06, 1.46]
Rogers 1998b	150	0.39 (3.1)	154	-0.97 (3.1)		21.2 %	1.36 [0.66, 2.06]
Seltzer 2004	91	1.33 (3.44)	55	0.09 (3.05)		8.9 %	1.24 [0.17, 2.31]
Tariot 2001	103	-0.1 (4.05)	102	-0.81 (4.03)		8.4 %	0.71 [-0.40, 1.82]
Winblad 2006	120	1.1 (3.3)	120	0.1 (3.3)		14.8 %	1.00 [0.17, 1.83]
Subtotal (95% CI)	**895**		**862**			**100.0 %**	**1.05 [0.73, 1.37]**

Heterogeneity: $Chi^2 = 5.28$, df = 6 (P = 0.51); $I^2 = 0.0\%$

Test for overall effect: Z = 6.43 (P < 0.00001)

Analysis 1.3. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 3 SIB (change from baseline at 24-26 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

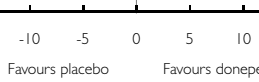
Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 3 SIB (change from baseline at 24-26 weeks) ITT-LOCF

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (10 mg/d) at 24 weeks							
Black 2007	166	0.19 (12.5)	155	-5.13 (12.6)		25.7 %	5.32 [2.57, 8.07]
Feldman 2001	139	2.22 (13.1)	145	-3.56 (14.72)		18.5 %	5.78 [2.54, 9.02]
Homma 2008	92	4.7 (11.2)	102	-4.2 (10.6)		20.5 %	8.90 [5.82, 11.98]
Jia 2017	150	2.9 (14.45)	151	-2 (14.75)		17.8 %	4.90 [1.60, 8.20]
Winblad 2006	128	2.6 (13.6)	120	-1.9 (13.1)		17.6 %	4.50 [1.18, 7.82]
Subtotal (95% CI)	**675**		**673**			**100.0 %**	**5.92 [4.53, 7.31]**

Heterogeneity: $Chi^2 = 4.86$, df = 4 (P = 0.30); $I^2 = 18\%$

Test for overall effect: Z = 8.33 (P < 0.00001)



Analysis 1.4. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 4 ADCS-ADL-severe (change from baseline at 24-26 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 4 ADCS-ADL-severe (change from baseline at 24-26 weeks) ITT-LOCF

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (10 mg/d) at 24 weeks							
Black 2007	151	-1.82 (6.6)	140	-2.53 (6.6)		29.2 %	0.71 [-0.81, 2.23]
Homma 2008	92	-0.3 (5.8)	102	-1.1 (5.1)		28.2 %	0.80 [-0.74, 2.34]
Winblad 2006	128	-1.5 (4.5)	120	-2.9 (5.5)		42.6 %	1.40 [0.14, 2.66]
Subtotal (95% CI)	**371**		**362**			**100.0 %**	**1.03 [0.21, 1.85]**
Heterogeneity: Chi^2 = 0.59, df = 2 (P = 0.74); I^2 =0.0%							
Test for overall effect: Z = 2.46 (P = 0.014)							

Analysis 1.5. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 5 CIBIC-Plus or CGIC (numbers improved at 24-26 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 5 CIBIC-Plus or CGIC (numbers improved at 24-26 weeks) ITT-LOCF

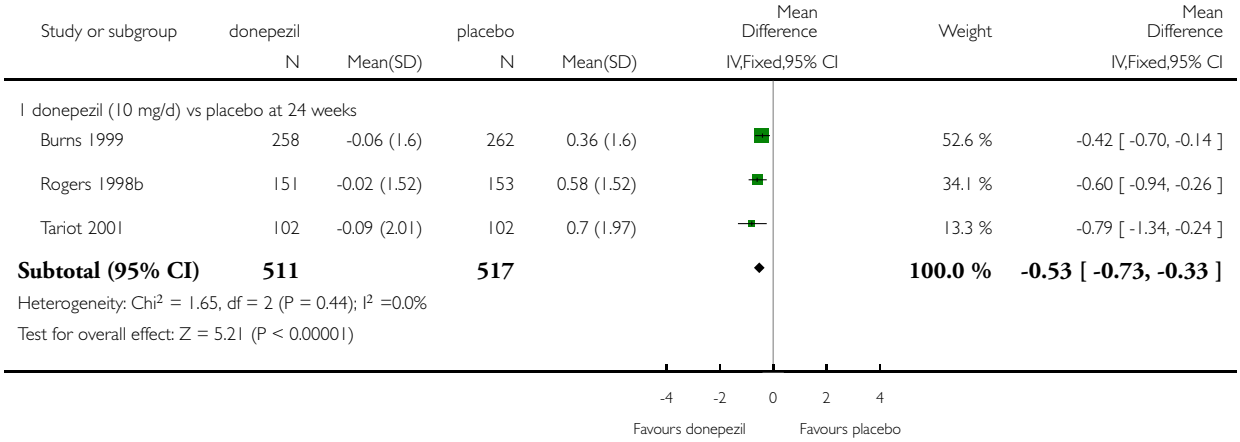
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	49/176	38/167		20.8 %	1.31 [0.80, 2.13]
Burns 1999	60/241	36/257		24.7 %	2.01 [1.29, 3.14]
Homma 2008	43/92	24/102		14.0 %	2.78 [1.54, 5.02]
Maher-Edwards 2011	28/65	17/55		9.0 %	1.67 [0.80, 3.50]
Rogers 1998b	37/149	17/152		14.2 %	2.52 [1.40, 4.54]
Winblad 2006	59/111	41/107		17.3 %	1.81 [1.07, 3.08]
Subtotal (95% CI)	**834**	**840**		**100.0 %**	**1.92 [1.54, 2.39]**
Total events: 276 (donepezil), 173 (placebo)					
Heterogeneity: Chi^2 = 4.94, df = 5 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 5.77 (P < 0.00001)					

Analysis 1.6. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 6 CDR-SB (change from baseline at 24-26 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 6 CDR-SB (change from baseline at 24-26 weeks) ITT-LOCF

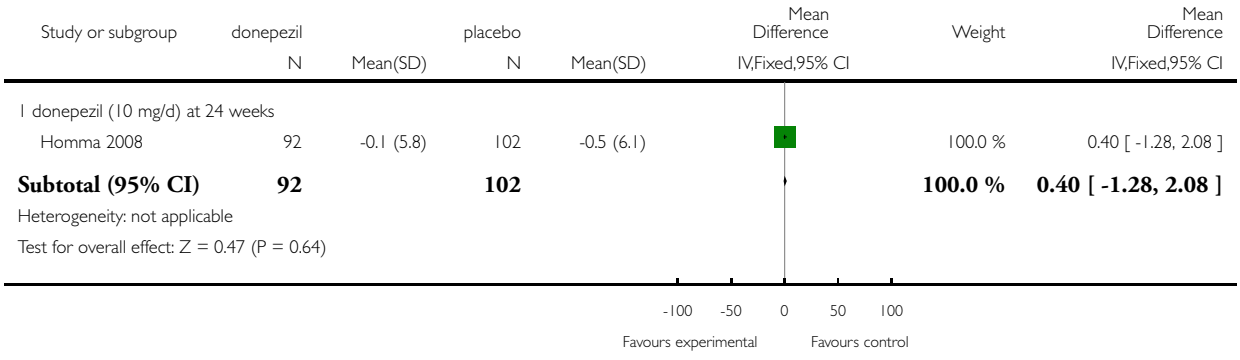


Analysis 1.7. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 7 BEHAVE-AD (change from baseline at 24-26 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 7 BEHAVE-AD (change from baseline at 24-26 weeks) ITT-LOCF



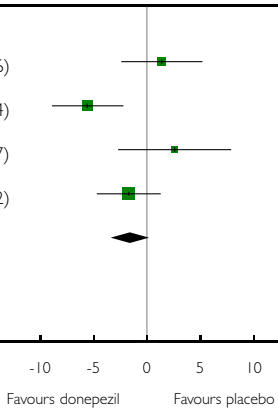
Analysis 1.8. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 8 Behavioural disturbance (Total NPI) (change from baseline at 24-26 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 8 Behavioural disturbance (Total NPI) (change from baseline at 24-26 weeks) ITT-LOCF

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (10 mg/d) at 24 weeks							
Black 2007	153	-1.91 (16.5)	144	-3.31 (16.6)		23.2 %	1.40 [-2.37, 5.17]
Feldman 2001	138	-4.6 (14.29)	144	1 (14.4)		29.4 %	-5.60 [-8.95, -2.25]
Tariot 2001	103	-2.3 (19.47)	105	-4.9 (19.47)		11.8 %	2.60 [-2.69, 7.89]
Winblad 2006	128	-3.8 (12.4)	120	-2.1 (12)		35.7 %	-1.70 [-4.74, 1.34]
Subtotal (95% CI)	**522**		**513**			**100.0 %**	**-1.62 [-3.43, 0.19]**
Heterogeneity: Chi^2 = 10.34, df = 3 (P = 0.02); I^2 =71%							
Test for overall effect: Z = 1.75 (P = 0.080)							

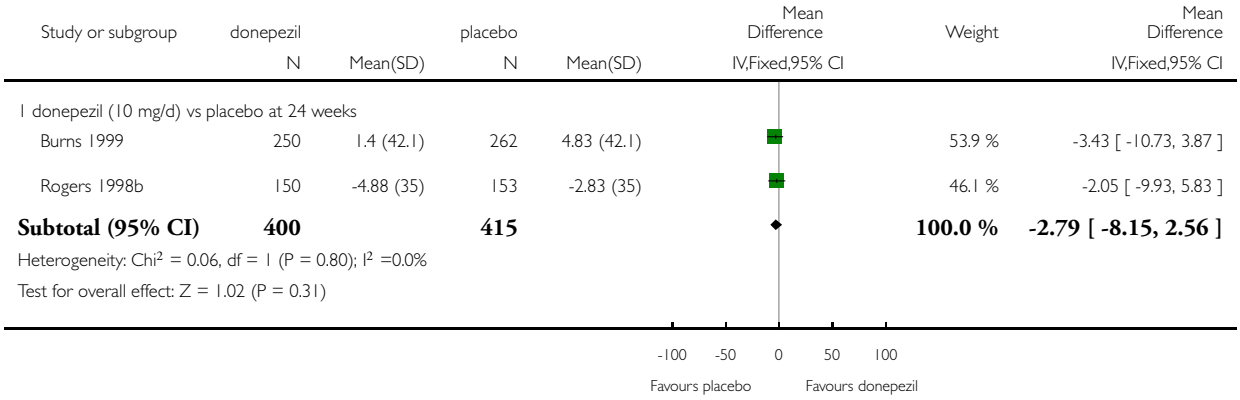


Analysis 1.9. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 9 QoL (participant-rated quality of life at 24-26 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 9 QoL (participant-rated quality of life at 24-26 weeks) ITT-LOCF



Analysis 1.10. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 10 Total number of withdrawals before end of treatment at 24-26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 10 Total number of withdrawals before end of treatment at 24-26 weeks

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	59/176	40/167		14.5 %	1.59 [1.00, 2.54]
Burns 1999	72/273	55/274		20.1 %	1.42 [0.96, 2.12]
Feldman 2001	23/144	20/147		7.6 %	1.21 [0.63, 2.30]
Homma 2008	20/96	19/105		6.5 %	1.19 [0.59, 2.39]
Jia 2017	29/157	30/156		9.9 %	0.95 [0.54, 1.68]
Krishnan 2003	6/34	10/33		2.5 %	0.50 [0.17, 1.54]
Maher-Edwards 2011	10/67	15/61		4.2 %	0.54 [0.23, 1.30]
Rogers 1998b	51/157	32/162		12.7 %	1.93 [1.17, 3.19]
Seltzer 2004	26/96	11/57		5.4 %	1.52 [0.71, 3.27]
Tariot 2001	19/103	27/105		7.4 %	0.66 [0.34, 1.26]
Tune 2003	0/14	2/14		0.4 %	0.13 [0.01, 2.11]
Winblad 2006	33/128	21/120		8.7 %	1.62 [0.89, 2.96]
Subtotal (95% CI)	**1445**	**1401**		**100.0 %**	**1.25 [1.05, 1.50]**
Total events: 348 (donepezil), 282 (placebo)					
Heterogeneity: Chi^2 = 18.61, df = 11 (P = 0.07); I^2 =41%					
Test for overall effect: Z = 2.49 (P = 0.013)					

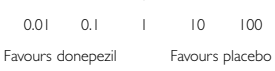
Analysis 1.11. Comparison 1 Donepezil (10 mg/day) versus placebo, Outcome 11 Total number of participants who suffered from at least one adverse event by 24-26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 1 Donepezil (10 mg/day) versus placebo

Outcome: 11 Total number of participants who suffered from at least one adverse event by 24-26 weeks

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	140/176	117/167		16.1 %	1.66 [1.01, 2.72]
Burns 1999	234/273	207/274		19.4 %	1.94 [1.25, 3.01]
Feldman 2001	120/144	117/147		12.7 %	1.28 [0.71, 2.32]
Homma 2008	80/96	77/105		8.0 %	1.82 [0.91, 3.62]
Jia 2017	42/157	26/156		12.5 %	1.83 [1.05, 3.16]
Krishnan 2003	0/34	1/33		1.0 %	0.31 [0.01, 7.99]
Maher-Edwards 2011	26/67	18/62		7.5 %	1.55 [0.74, 3.24]
Seltzer 2004	67/96	37/57		9.2 %	1.25 [0.62, 2.51]
Tariot 2001	99/103	102/105		2.6 %	0.73 [0.16, 3.34]
Winblad 2006	105/128	91/120		11.1 %	1.45 [0.79, 2.69]
Subtotal (95% CI)	**1274**	**1226**		**100.0 %**	**1.59 [1.31, 1.95]**
Total events: 913 (donepezil), 793 (placebo)					
Heterogeneity: Chi^2 = 4.25, df = 9 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 4.56 (P < 0.00001)					



Analysis 2.1. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 1 ADAS-COG (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 1 ADAS-COG (change from baseline) completers

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks							
Homma 1998	49	-2.99 (5.67)	52	-1.89 (5.55)		6.1 %	-1.10 [-3.29, 1.09]
Homma 2000	124	-3.04 (6.01)	110	-0.74 (5.87)		12.5 %	-2.30 [-3.82, -0.78]
Rogers 1996	35	-2.13 (4.91)	36	1.04 (4.68)		5.8 %	-3.17 [-5.40, -0.94]
Rogers 1998a	141	-2.23 (5.46)	139	0.4 (5.42)		17.9 %	-2.63 [-3.90, -1.36]
Rogers 1998b	141	-1.28 (5.34)	137	0.84 (5.38)		18.3 %	-2.12 [-3.38, -0.86]
Burns 1999	235	-1.55 (4.75)	242	0.36 (4.82)		39.4 %	-1.91 [-2.77, -1.05]
Subtotal (95% CI)	**725**		**716**			**100.0 %**	**-2.15 [-2.69, -1.61]**
Heterogeneity: Chi² = 2.57, df = 5 (P = 0.77); I² =0.0%							
Test for overall effect: Z = 7.82 (P < 0.00001)							
2 donepezil (5 mg/d) vs placebo at 24 weeks							
Homma 2000	114	-2.92 (6.41)	101	0.37 (6.23)		20.0 %	-3.29 [-4.98, -1.60]
Rogers 1998b	130	-0.9 (5.81)	132	1.81 (5.86)		28.6 %	-2.71 [-4.12, -1.30]
Burns 1999	212	0.31 (5.53)	217	1.45 (5.6)		51.5 %	-1.14 [-2.19, -0.09]
Subtotal (95% CI)	**456**		**450**			**100.0 %**	**-2.02 [-2.77, -1.26]**
Heterogeneity: Chi² = 5.76, df = 2 (P = 0.06); I² =65%							
Test for overall effect: Z = 5.23 (P < 0.00001)							
3 donepezil (10 mg/d) vs placebo at 12 weeks							
Seltzer 2004	79	-1.5 (5.4)	51	0.39 (4.74)		10.1 %	-1.89 [-3.65, -0.13]
Tune 2003	14	-3.98 (3.52)	13	-2.95 (3.53)		4.4 %	-1.03 [-3.69, 1.63]
Krishnan 2003	31	-1.99 (5.07)	30	1.39 (5.04)		4.9 %	-3.38 [-5.92, -0.84]
Rogers 1998a	125	-2.77 (5.48)	139	0.4 (5.42)		18.1 %	-3.17 [-4.49, -1.85]
Rogers 1998b	125	-1.86 (5.25)	137	0.84 (5.38)		19.0 %	-2.70 [-3.99, -1.41]
Burns 1999	220	-1.91 (4.75)	242	0.36 (4.82)		41.2 %	-2.27 [-3.14, -1.40]
Study 306	20	-0.15 (5.63)	19	1.06 (6.28)		2.2 %	-1.21 [-4.96, 2.54]
Subtotal (95% CI)	**614**		**631**			**100.0 %**	**-2.45 [-3.01, -1.89]**
Heterogeneity: Chi² = 3.87, df = 6 (P = 0.69); I² =0.0%							

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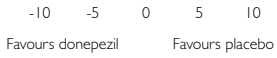
Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Test for overall effect: Z = 8.57 (P < 0.00001)							
4 donepezil (10 mg/d) vs placebo at 24 weeks							
Seltzer 2004	67	-1.74 (4.97)	45	0.54 (4.5)		17.5 %	-2.28 [-4.05, -0.51]
Tune 2003	14	-3.65 (3.97)	13	-1.56 (3.97)		6.1 %	-2.09 [-5.09, 0.91]
Krishnan 2003	28	-0.59 (6.61)	28	3.35 (6.67)		4.6 %	-3.94 [-7.42, -0.46]
Rogers 1998b	105	-1.34 (5.84)	132	1.81 (5.86)		24.6 %	-3.15 [-4.65, -1.65]
Burns 1999	199	-1.36 (5.64)	217	1.45 (5.6)		47.2 %	-2.81 [-3.89, -1.73]
Subtotal (95% CI)	**413**		**435**			**100.0 %**	**-2.81 [-3.55, -2.06]**
Heterogeneity: Chi^2 = 1.17, df = 4 (P = 0.88); I^2 =0.0%							
Test for overall effect: Z = 7.41 (P < 0.00001)							



Analysis 2.2. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 2 ADAS-COG (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 2 ADAS-COG (change from baseline) ITT-LOCF

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks							
Homma 1998	51	-2.91 (4.95)	55	-1.87 (4.95)		22.1 %	-1.04 [-2.93, 0.85]
Rogers 1996	38	-2.23 (4.81)	40	0.98 (4.49)		18.4 %	-3.21 [-5.28, -1.14]
Rogers 1998a	154	-2.08 (5.11)	150	0.36 (5.11)		59.5 %	-2.44 [-3.59, -1.29]
Subtotal (95% CI)	**243**		**245**			**100.0 %**	**-2.27 [-3.16, -1.39]**
Heterogeneity: Chi^2 = 2.51, df = 2 (P = 0.28); I^2 =20%							
Test for overall effect: Z = 5.02 (P < 0.00001)							
2 donepezil (5 mg/d) vs placebo at 24 weeks							
Burns 1999	262	0.18 (5.5)	264	1.66 (5.5)		51.2 %	-1.48 [-2.42, -0.54]
Homma 2000	132	-2.19 (6.55)	126	0.52 (6.29)		18.4 %	-2.71 [-4.28, -1.14]
Rogers 1998b	152	-0.67 (5.43)	153	1.82 (5.43)		30.4 %	-2.49 [-3.71, -1.27]
Subtotal (95% CI)	**546**		**543**			**100.0 %**	**-2.01 [-2.69, -1.34]**
Heterogeneity: Chi^2 = 2.58, df = 2 (P = 0.27); I^2 =23%							
Test for overall effect: Z = 5.87 (P < 0.00001)							
3 donepezil (10 mg/d) vs placebo at 12 weeks							
Krishnan 2003	34	0.02 (6.47)	32	3.25 (6.34)		10.5 %	-3.23 [-6.32, -0.14]
Moraes 2006a	11	-4.8 (22.3)	12	2.5 (25.3)		0.3 %	-7.30 [-26.76, 12.16]
Rogers 1998a	153	-2.71 (5.11)	150	0.36 (5.11)		75.8 %	-3.07 [-4.22, -1.92]
Study 306	20	-0.15 (5.63)	19	1.06 (6.28)		7.1 %	-1.21 [-4.96, 2.54]
Tune 2003	14	-3.64 (5.39)	14	-0.16 (5.39)		6.3 %	-3.48 [-7.47, 0.51]
Subtotal (95% CI)	**232**		**227**			**100.0 %**	**-2.99 [-3.99, -1.99]**
Heterogeneity: Chi^2 = 1.15, df = 4 (P = 0.89); I^2 =0.0%							
Test for overall effect: Z = 5.85 (P < 0.00001)							
4 donepezil (10 mg/d) vs placebo at 24 weeks							
Burns 1999	254	-1.26 (5.5)	264	1.66 (5.5)		46.0 %	-2.92 [-3.87, -1.97]
Maher-Edwards 2011	67	-1.5 (6)	61	-0.3 (6.26)		9.1 %	-1.20 [-3.33, 0.93]
Moraes 2006b	17	-7.3 (18.4)	18	3.8 (26.3)		0.2 %	-11.10 [-26.07, 3.87]
Rogers 1998b	150	-1.06 (5.43)	153	1.82 (5.43)		27.6 %	-2.88 [-4.10, -1.66]

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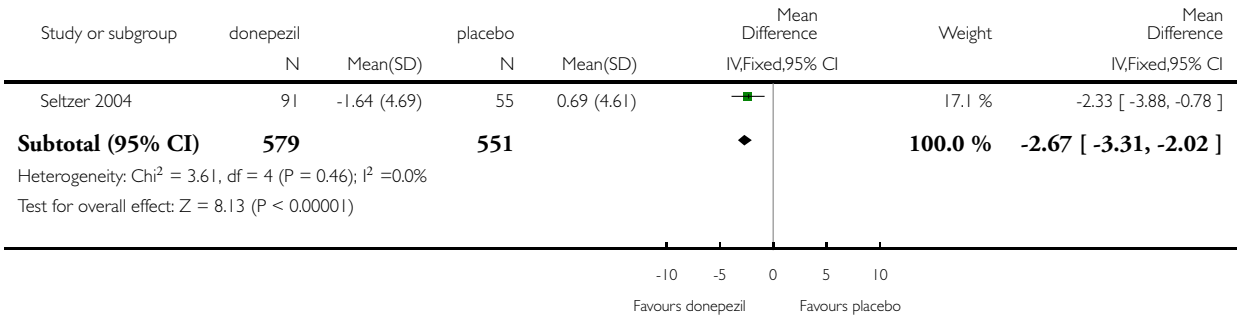
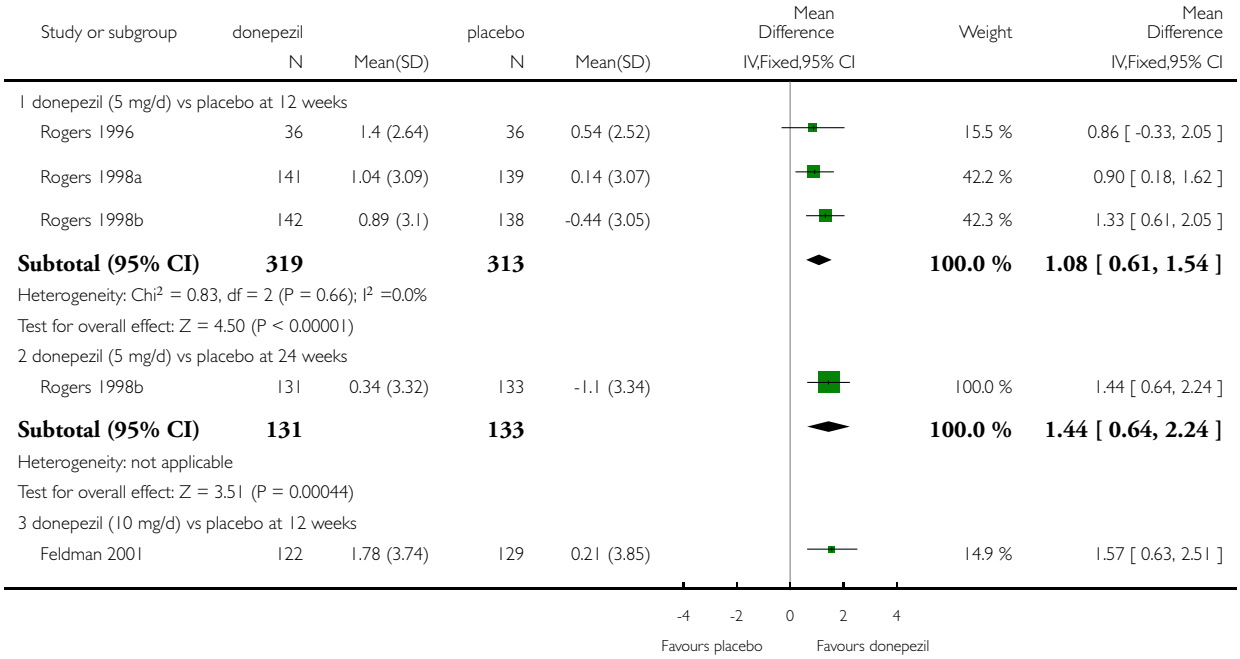


Analysis 2.3. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 3 MMSE (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 3 MMSE (change from baseline) completers



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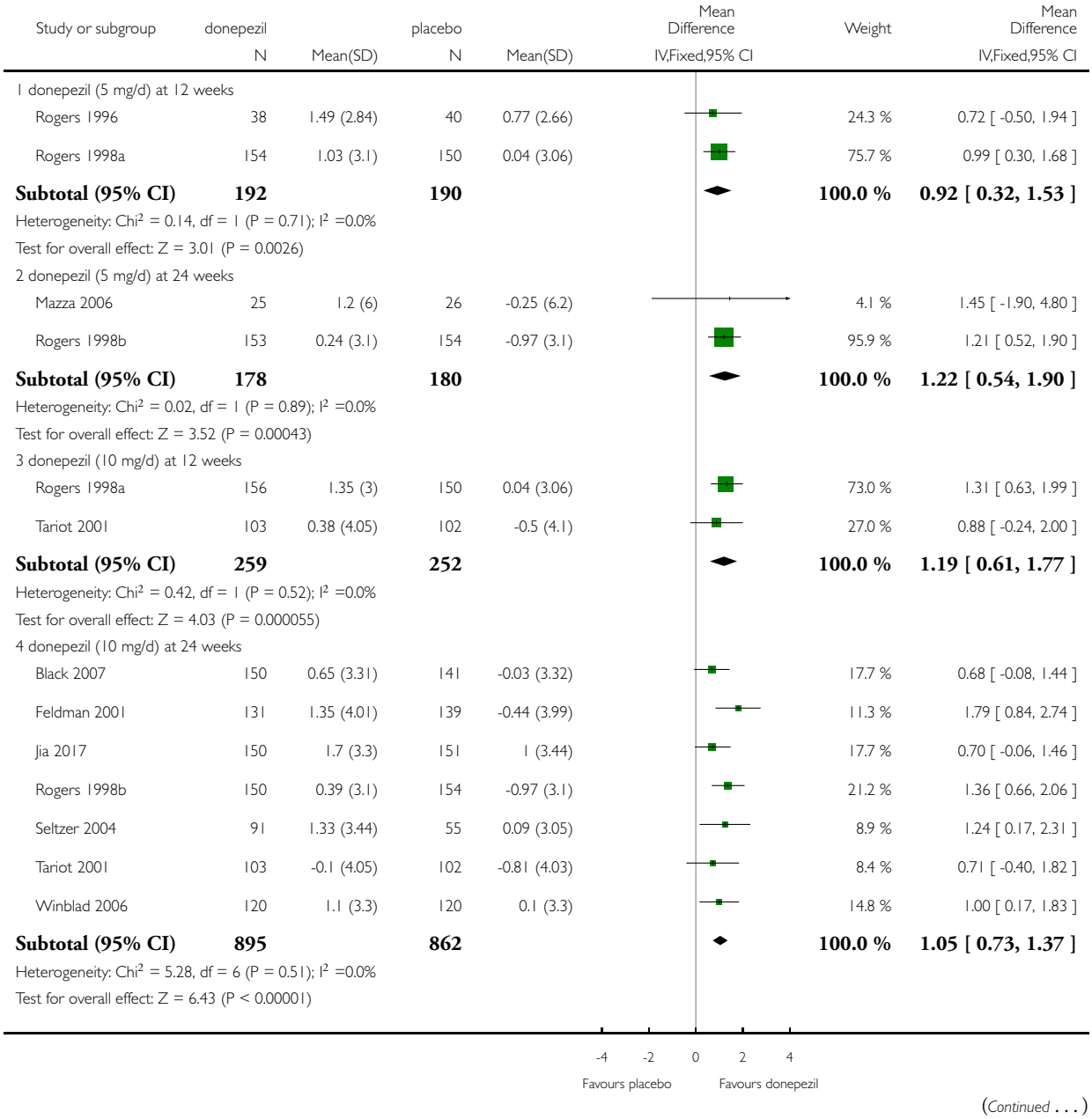
Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Rogers 1998a	125	1.3 (3.13)	139	0.14 (3.07)		23.3 %	1.16 [0.41, 1.91]
Rogers 1998b	124	1.05 (3.12)	138	-0.44 (3.05)		23.4 %	1.49 [0.74, 2.24]
Seltzer 2004	79	1.6 (3.21)	51	0.39 (2.57)		13.1 %	1.21 [0.21, 2.21]
Study 205	6	3.52 (3.26)	5	-0.83 (3.33)		0.9 %	4.35 [0.44, 8.26]
Winblad 2001	127	0.69 (2.89)	128	-0.18 (3.08)		24.4 %	0.87 [0.14, 1.60]
Subtotal (95% CI)	**583**		**590**			**100.0 %**	**1.26 [0.90, 1.62]**
Heterogeneity: Chi^2 = 4.34, df = 5 (P = 0.50); I^2 =0.0%							
Test for overall effect: Z = 6.83 (P < 0.00001)							
4 donepezil (10 mg/d) vs placebo at 24 weeks							
Black 2007	111	0.76 (3.27)	119	0.02 (3.27)		21.9 %	0.74 [-0.11, 1.59]
Feldman 2001	119	1.17 (4)	124	-0.27 (4.09)		15.1 %	1.44 [0.42, 2.46]
Rogers 1998b	105	0.44 (3.38)	133	-1.1 (3.34)		21.1 %	1.54 [0.68, 2.40]
Seltzer 2004	67	1.48 (3.18)	45	0.28 (3.21)		10.7 %	1.20 [-0.01, 2.41]
Winblad 2001	121	0.43 (3.97)	120	-1.08 (3.25)		18.6 %	1.51 [0.59, 2.43]
Winblad 2006	95	1.5 (3.9)	98	0.1 (4)		12.6 %	1.40 [0.29, 2.51]
Subtotal (95% CI)	**618**		**639**			**100.0 %**	**1.29 [0.90, 1.69]**
Heterogeneity: Chi^2 = 2.31, df = 5 (P = 0.80); I^2 =0.0%							
Test for overall effect: Z = 6.40 (P < 0.00001)							
5 donepezil (10 mg/d) vs placebo at 52 weeks							
Winblad 2001	91	-0.36 (4.58)	98	-2.2 (4.59)		100.0 %	1.84 [0.53, 3.15]
Subtotal (95% CI)	**91**		**98**			**100.0 %**	**1.84 [0.53, 3.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.76 (P = 0.0058)							

Analysis 2.4. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 4 MMSE (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 4 MMSE (change from baseline) ITT-LOCF



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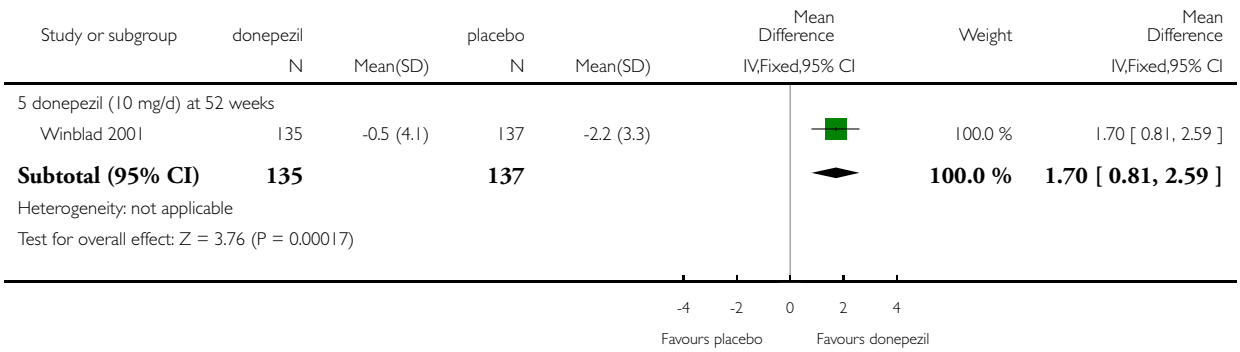
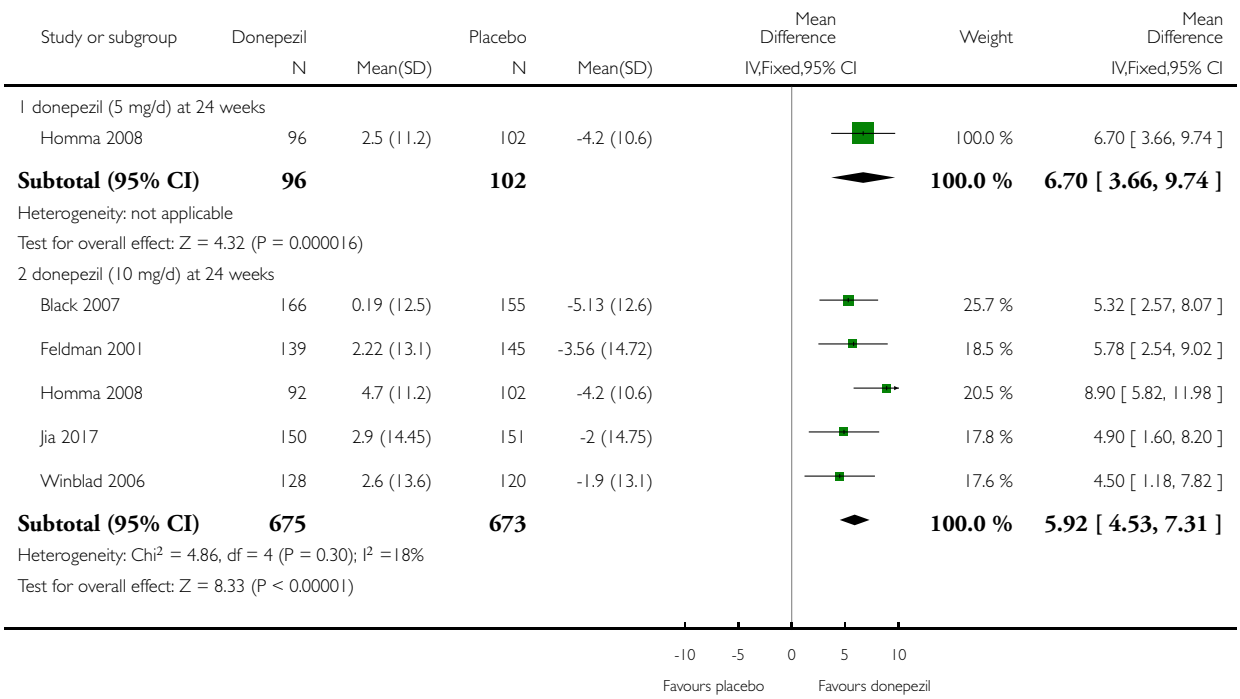


Analysis 2.5. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 5 SIB (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 5 SIB (change from baseline) ITT-LOCF



Analysis 2.6. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 6 CIBIC-plus or CGIC (numbers improved) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 6 CIBIC-plus or CGIC (numbers improved) completers

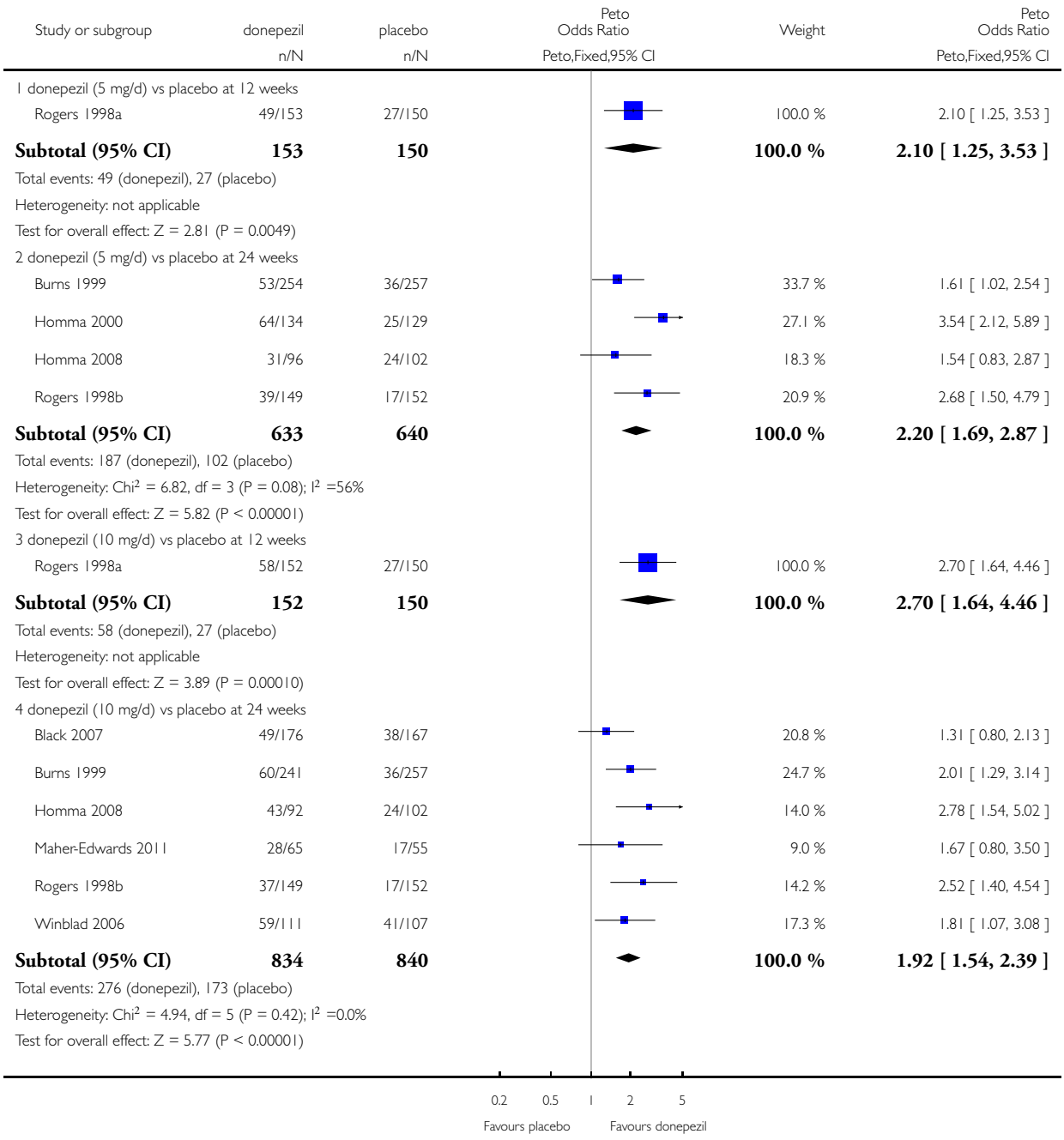
Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 24 weeks					
Homma 2000	60/116	24/112		100.0 %	3.93 [2.20, 7.02]
Subtotal (95% CI)	**116**	**112**		**100.0 %**	**3.93 [2.20, 7.02]**
Total events: 60 (donepezil), 24 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.62 (P < 0.00001)					
2 donepezil (10 mg/d) vs placebo at 24 weeks					
Winblad 2006	57/97	36/99		100.0 %	2.49 [1.40, 4.43]
Subtotal (95% CI)	**97**	**99**		**100.0 %**	**2.49 [1.40, 4.43]**
Total events: 57 (donepezil), 36 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.11 (P = 0.0019)					

Analysis 2.7. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 7 CIBIC-plus or CGIC (numbers improved) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 7 CIBIC-plus or CGIC (numbers improved) ITT-LOCF



Analysis 2.8. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 8 CDR-SB (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 8 CDR-SB (change from baseline) completers

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks							
Homma 1998	50	-0.31 (1.7)	54	-0.26 (1.32)		4.8 %	-0.05 [-0.64, 0.54]
Homma 2000	128	-0.16 (1.13)	119	0.19 (1.09)		21.9 %	-0.35 [-0.63, -0.07]
Rogers 1996	36	0.06 (1.2)	36	0.22 (1.14)		5.7 %	-0.16 [-0.70, 0.38]
Rogers 1998a	141	-0.09 (1.42)	139	-0.1 (1.41)		15.3 %	0.01 [-0.32, 0.34]
Rogers 1998b	142	-0.22 (1.31)	138	0.07 (1.29)		18.1 %	-0.29 [-0.59, 0.01]
Burns 1999	234	-0.18 (1.22)	244	0.15 (1.25)		34.2 %	-0.33 [-0.55, -0.11]
Subtotal (95% CI)	**731**		**730**			**100.0 %**	**-0.25 [-0.38, -0.12]**
Heterogeneity: Chi^2 = 3.98, df = 5 (P = 0.55); I^2 =0.0%							
Test for overall effect: Z = 3.81 (P = 0.00014)							
2 donepezil (5 mg/d) vs placebo at 24 weeks							
Homma 2000	119	-0.08 (1.64)	109	0.83 (1.57)		28.0 %	-0.91 [-1.33, -0.49]
Rogers 1998b	131	-0.02 (1.72)	133	0.63 (1.73)		28.1 %	-0.65 [-1.07, -0.23]
Burns 1999	211	0.06 (1.74)	217	0.39 (1.77)		44.0 %	-0.33 [-0.66, 0.00]
Subtotal (95% CI)	**461**		**459**			**100.0 %**	**-0.58 [-0.80, -0.36]**
Heterogeneity: Chi^2 = 4.69, df = 2 (P = 0.10); I^2 =57%							
Test for overall effect: Z = 5.17 (P < 0.00001)							
3 donepezil (10 mg/d) vs placebo at 12 weeks							
Rogers 1998b	124	-0.06 (1.34)	138	0.07 (1.29)		24.0 %	-0.13 [-0.45, 0.19]
Rogers 1998a	124	-0.35 (1.34)	139	-0.1 (1.41)		22.1 %	-0.25 [-0.58, 0.08]
Study 205	6	-0.89 (0.86)	5	-0.03 (0.85)		2.4 %	-0.86 [-1.87, 0.15]
Burns 1999	219	-0.19 (1.18)	244	0.15 (1.25)		49.8 %	-0.34 [-0.56, -0.12]
Study 306	20	0.06 (1.12)	19	-0.01 (2.39)		1.7 %	0.07 [-1.11, 1.25]
Subtotal (95% CI)	**493**		**545**			**100.0 %**	**-0.27 [-0.43, -0.12]**

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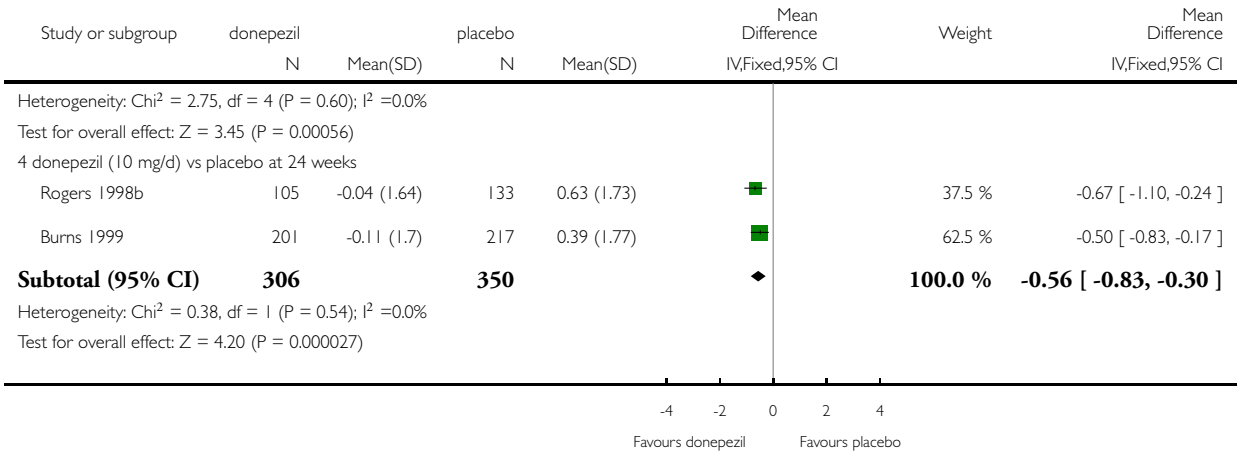
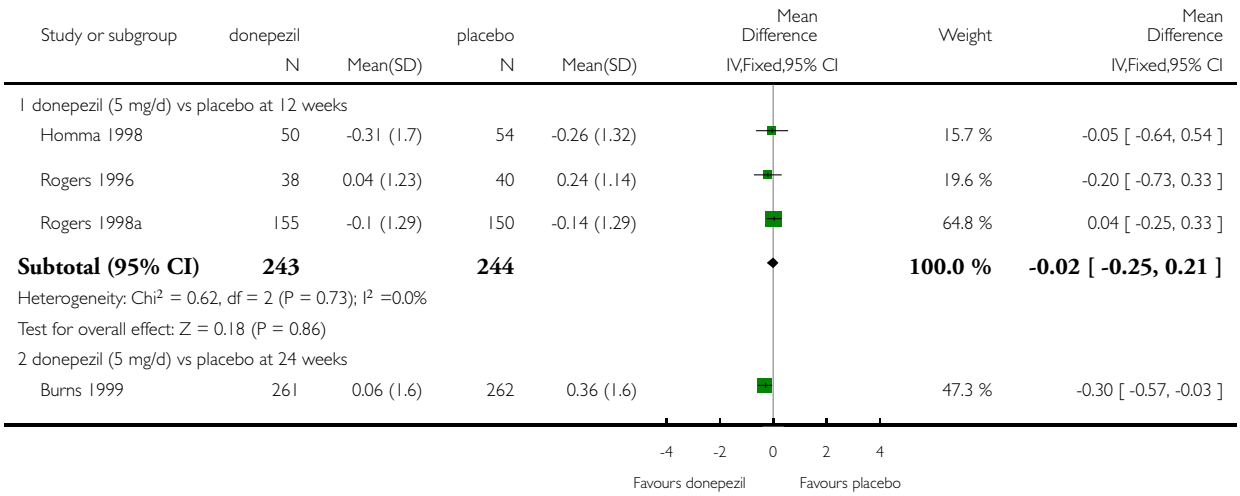


Analysis 2.9. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 9 CDR-SB (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 9 CDR-SB (change from baseline) ITT-LOCF



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Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Homma 2000	134	0 (1.74)	129	0.86 (1.59)		21.9 %	-0.86 [-1.26, -0.46]
Rogers 1998b	154	-0.01 (1.52)	153	0.58 (1.52)		30.8 %	-0.59 [-0.93, -0.25]
Subtotal (95% CI)	**549**		**544**			**100.0 %**	**-0.51 [-0.70, -0.32]**
Heterogeneity: Chi^2 = 5.37, df = 2 (P = 0.07); I^2 =63%							
Test for overall effect: Z = 5.32 (P < 0.00001)							
3 donepezil (10 mg/d) vs placebo at 12 weeks							
Rogers 1998a	154	-0.31 (1.29)	150	-0.14 (1.29)		67.0 %	-0.17 [-0.46, 0.12]
Study 205	6	-0.83 (0.91)	6	0.25 (0.91)		5.3 %	-1.08 [-2.11, -0.05]
Study 306	20	0.06 (1.12)	19	-0.01 (1.31)		9.6 %	0.07 [-0.70, 0.84]
Tariot 2001	102	-0.18 (2.14)	102	0.2 (1.92)		18.1 %	-0.38 [-0.94, 0.18]
Subtotal (95% CI)	**282**		**277**			**100.0 %**	**-0.23 [-0.47, 0.00]**
Heterogeneity: Chi^2 = 3.65, df = 3 (P = 0.30); I^2 =18%							
Test for overall effect: Z = 1.93 (P = 0.054)							
4 donepezil (10 mg/d) vs placebo at 24 weeks							
Burns 1999	258	-0.06 (1.6)	262	0.36 (1.6)		52.6 %	-0.42 [-0.70, -0.14]
Rogers 1998b	151	-0.02 (1.52)	153	0.58 (1.52)		34.1 %	-0.60 [-0.94, -0.26]
Tariot 2001	102	-0.09 (2.01)	102	0.7 (1.97)		13.3 %	-0.79 [-1.34, -0.24]
Subtotal (95% CI)	**511**		**517**			**100.0 %**	**-0.53 [-0.73, -0.33]**
Heterogeneity: Chi^2 = 1.65, df = 2 (P = 0.44); I^2 =0.0%							
Test for overall effect: Z = 5.21 (P < 0.00001)							

Analysis 2.10. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 10 GBS or MENFIS - global assessment completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 10 GBS or MENFIS - global assessment completers

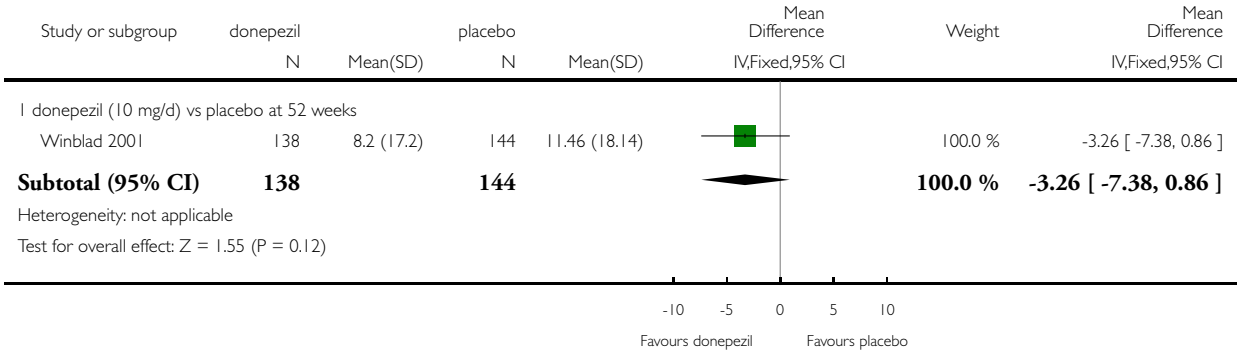
Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 24 weeks							
Homma 2000	116	-0.72 (5.71)	112	1.84 (7.3)		100.0 %	-2.56 [-4.27, -0.85]
Subtotal (95% CI)	**116**		**112**			**100.0 %**	**-2.56 [-4.27, -0.85]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.94 (P = 0.0033)							
2 donepezil (10 mg/d) vs placebo at 12 weeks							
Winblad 2001	129	1.52 (12.31)	129	2.6 (12.87)		100.0 %	-1.08 [-4.15, 1.99]
Subtotal (95% CI)	**129**		**129**			**100.0 %**	**-1.08 [-4.15, 1.99]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							
3 donepezil (10 mg/d) vs placebo at 24 weeks							
Winblad 2001	122	1.71 (14.15)	121	4.87 (15.17)		100.0 %	-3.16 [-6.85, 0.53]
Subtotal (95% CI)	**122**		**121**			**100.0 %**	**-3.16 [-6.85, 0.53]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.68 (P = 0.093)							
4 donepezil (10 mg/d) vs placebo at 52 weeks							
Winblad 2001	93	7.38 (20.25)	97	13.39 (21.35)		100.0 %	-6.01 [-11.93, -0.09]
Subtotal (95% CI)	**93**		**97**			**100.0 %**	**-6.01 [-11.93, -0.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.99 (P = 0.046)							

Analysis 2.11. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 11 GBS - global assessment ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 11 GBS - global assessment ITT-LOCF

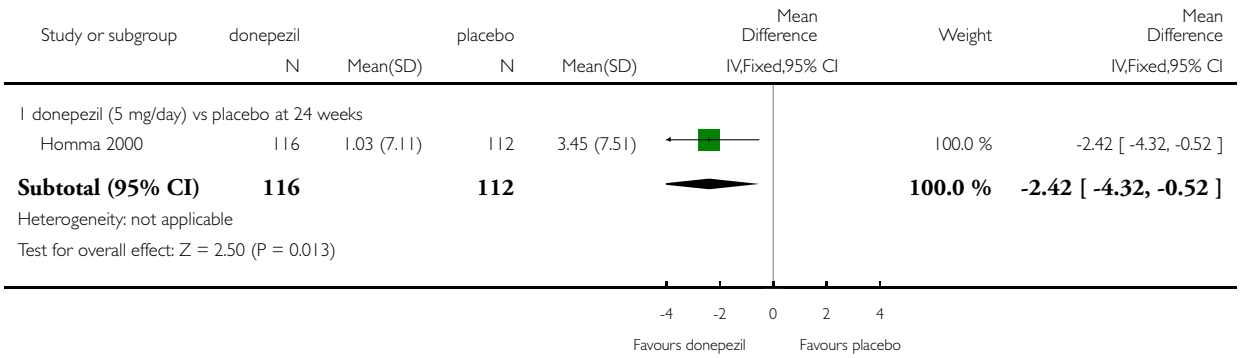


Analysis 2.12. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 12 ADL and IADL (CMCS) (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 12 ADL and IADL (CMCS) (change from baseline) completers

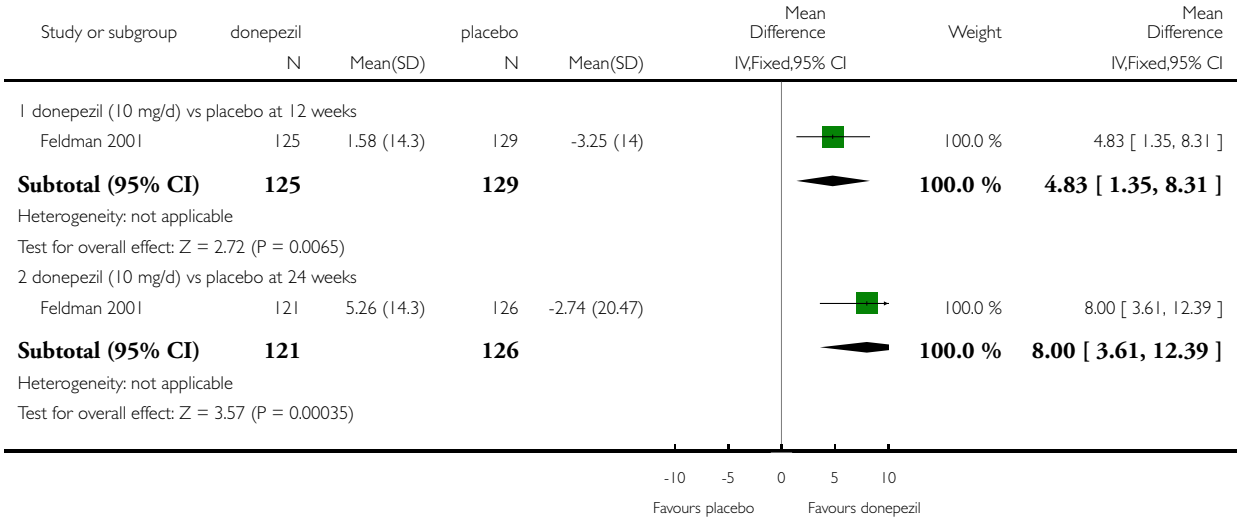


Analysis 2.13. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 13 ADI and IADL (DAD) (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 13 ADI and IADL (DAD) (change from baseline) completers



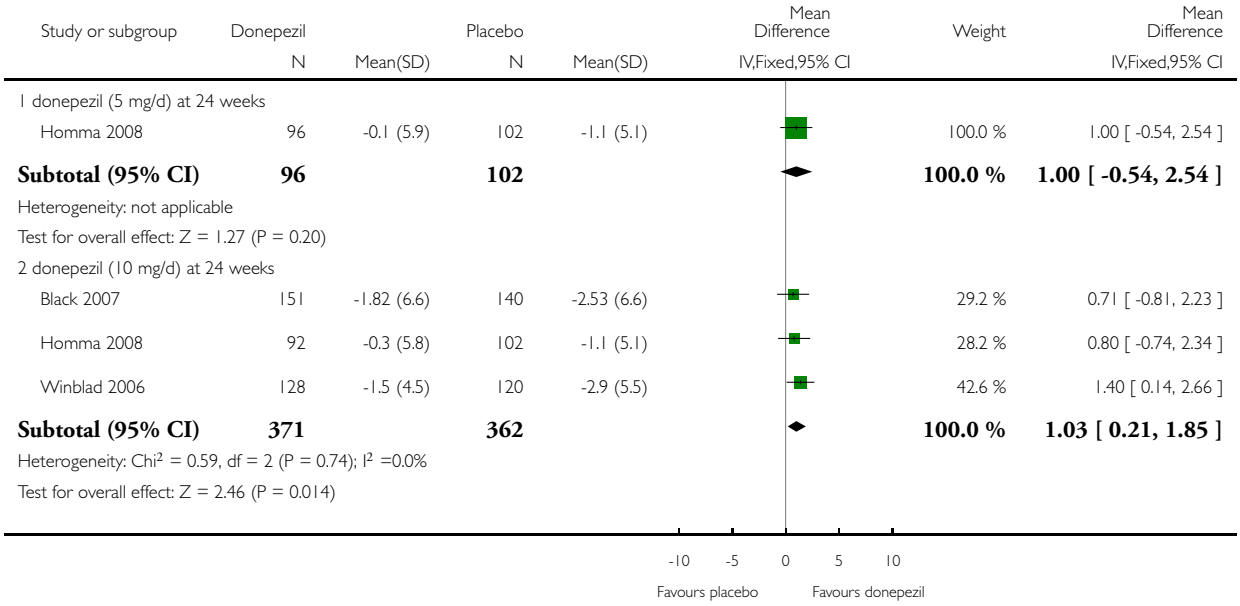
Analysis 2.14. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 14 ADCS-ADL-severe (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 14 ADCS-ADL-severe (change from baseline) ITT-LOCF

Study or subgroup	Donepezil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) at 24 weeks							
Homma 2008	96	-0.1 (5.9)	102	-1.1 (5.1)		100.0 %	1.00 [-0.54, 2.54]
Subtotal (95% CI)	**96**		**102**			**100.0 %**	**1.00 [-0.54, 2.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.27 (P = 0.20)							
2 donepezil (10 mg/d) at 24 weeks							
Black 2007	151	-1.82 (6.6)	140	-2.53 (6.6)		29.2 %	0.71 [-0.81, 2.23]
Homma 2008	92	-0.3 (5.8)	102	-1.1 (5.1)		28.2 %	0.80 [-0.74, 2.34]
Winblad 2006	128	-1.5 (4.5)	120	-2.9 (5.5)		42.6 %	1.40 [0.14, 2.66]
Subtotal (95% CI)	**371**		**362**			**100.0 %**	**1.03 [0.21, 1.85]**
Heterogeneity: Chi^2 = 0.59, df = 2 (P = 0.74); I^2 =0.0%							
Test for overall effect: Z = 2.46 (P = 0.014)							

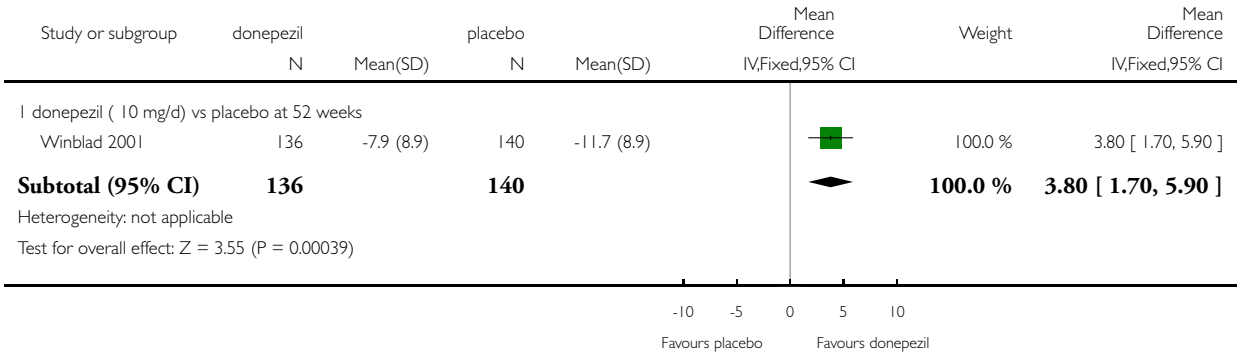


Analysis 2.15. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 15 PDS - progressive deterioration scale ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 15 PDS - progressive deterioration scale ITT-LOCF

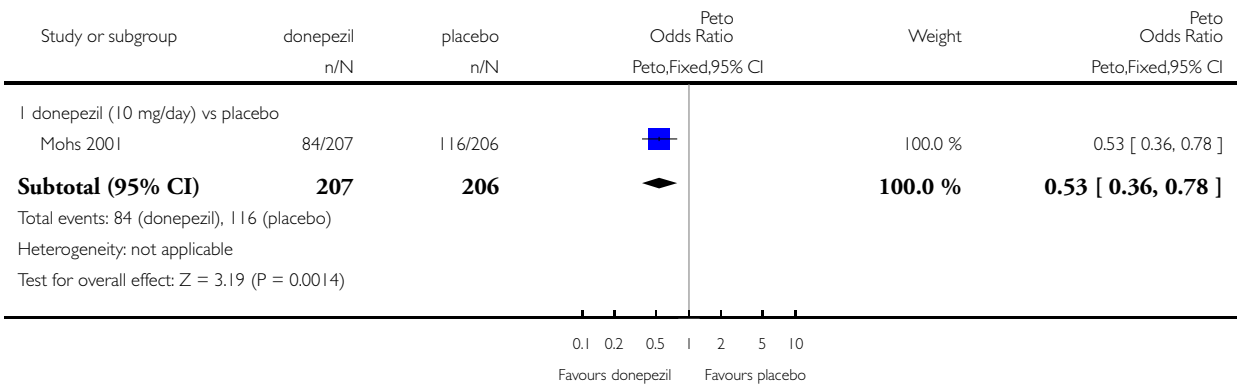


Analysis 2.16. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 16 Total number meeting criterion for functional decline before end of treatment.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 16 Total number meeting criterion for functional decline before end of treatment

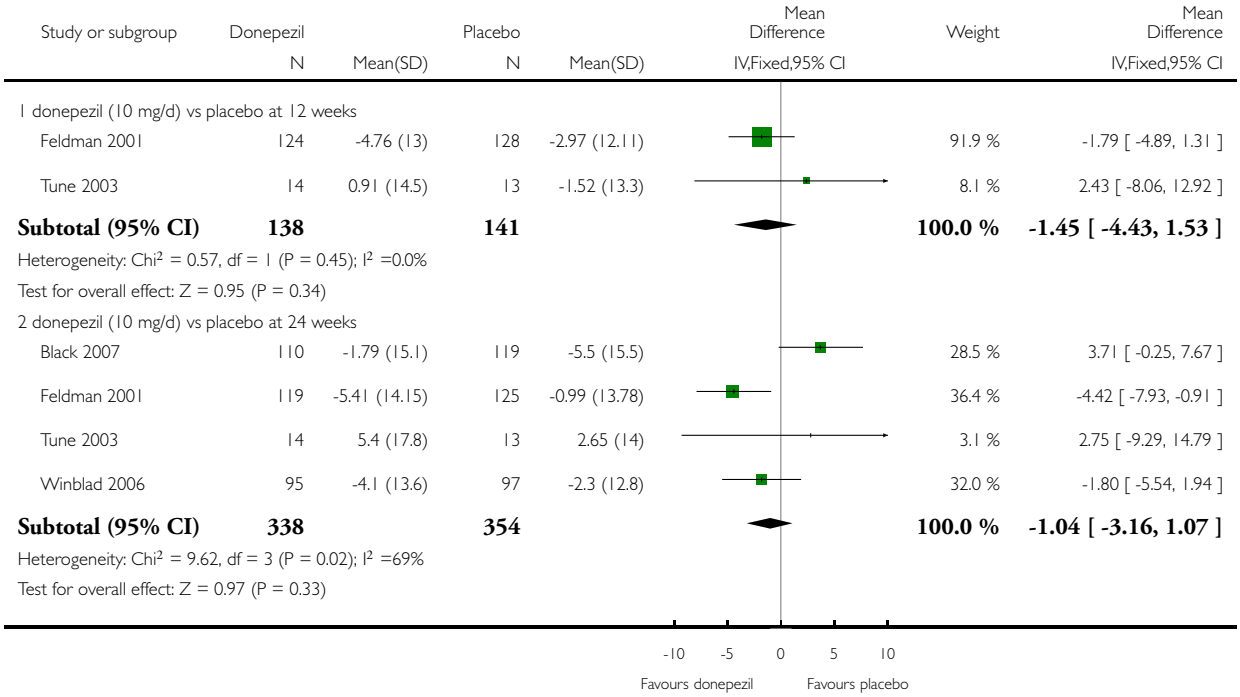


Analysis 2.17. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 17 Behavioural disturbance (total NPI) (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 17 Behavioural disturbance (total NPI) (change from baseline) completers



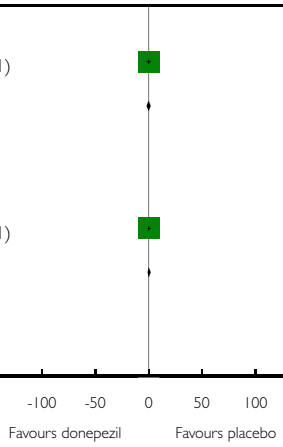
Analysis 2.18. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 18 BEHAVE-AD (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 18 BEHAVE-AD (change from baseline) ITT-LOCF

Study or subgroup	Donepezil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) at 24 weeks							
Homma 2008	96	-0.5 (5.9)	102	-0.5 (6.1)		100.0 %	0.0 [-1.67, 1.67]
Subtotal (95% CI)	**96**		**102**			**100.0 %**	**0.0 [-1.67, 1.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 donepezil (10 mg/d) at 24 weeks							
Homma 2008	92	-0.1 (5.8)	102	-0.5 (6.1)		100.0 %	0.40 [-1.28, 2.08]
Subtotal (95% CI)	**92**		**102**			**100.0 %**	**0.40 [-1.28, 2.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.47 (P = 0.64)							

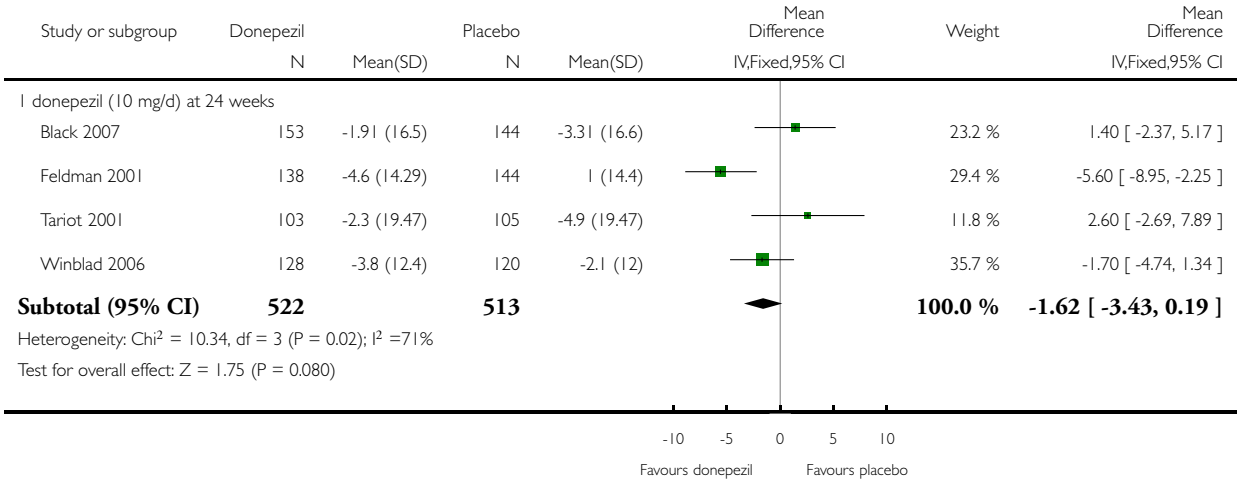


Analysis 2.19. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 19 Behavioural disturbance (total NPI) (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 19 Behavioural disturbance (total NPI) (change from baseline) ITT-LOCF



Analysis 2.20. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 20 QoL (participant-rated quality of life) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 20 QoL (participant-rated quality of life) completers

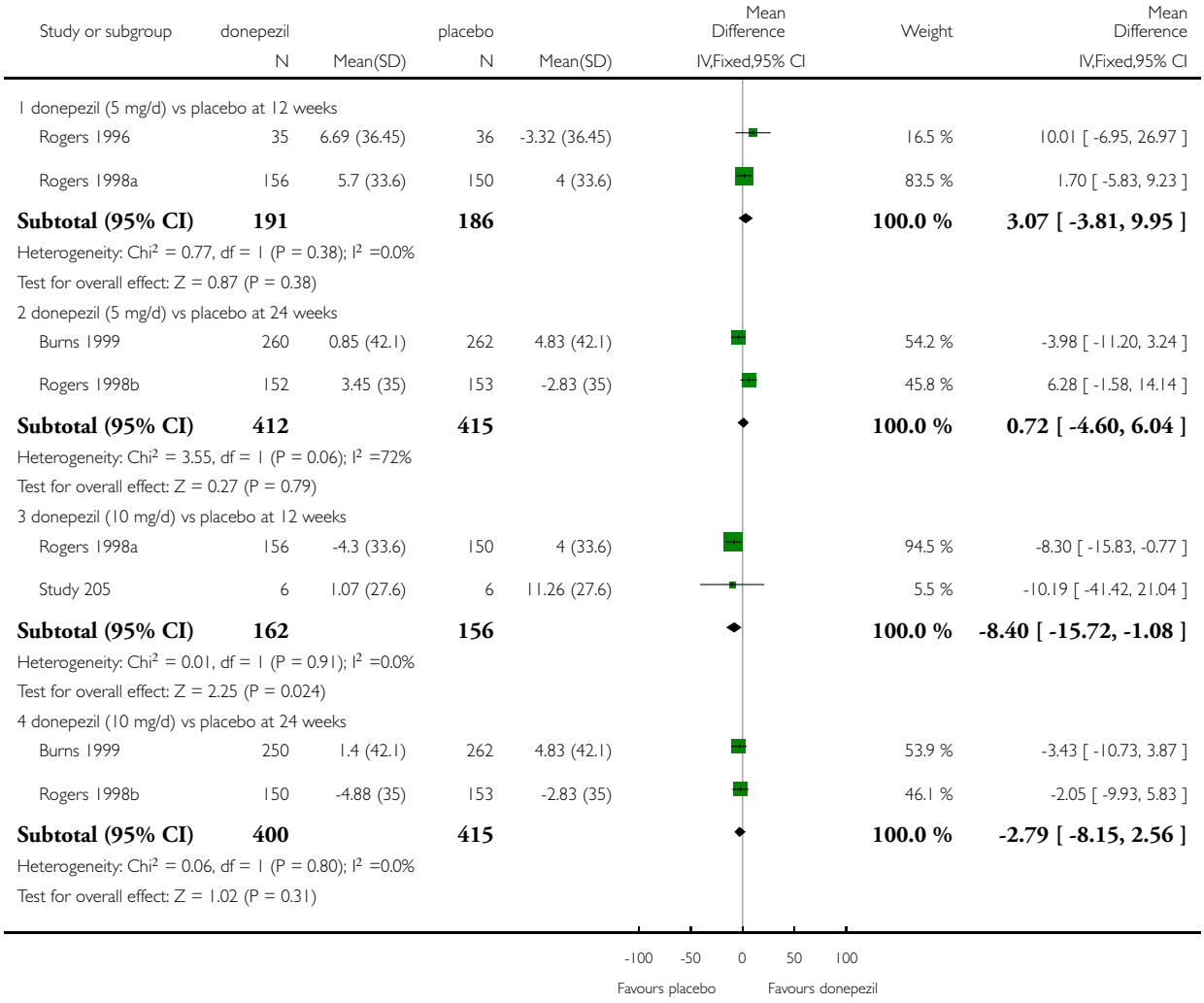
Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks							
Burns 1999	231	2.77 (36.93)	241	3.75 (37.1)		39.9 %	-0.98 [-7.66, 5.70]
Rogers 1996	35	6.69 (43.9)	36	-3.32 (41.7)		4.5 %	10.01 [-9.92, 29.94]
Rogers 1998a	156	-5.7 (33.6)	150	-4 (33.6)		31.4 %	-1.70 [-9.23, 5.83]
Rogers 1998b	141	8.18 (36.22)	137	1.34 (36.75)		24.2 %	6.84 [-1.74, 15.42]
Subtotal (95% CI)	**563**		**564**			**100.0 %**	**1.18 [-3.04, 5.40]**
Heterogeneity: Chi² = 3.39, df = 3 (P = 0.34); I² =11%							
Test for overall effect: Z = 0.55 (P = 0.58)							
2 donepezil (5 mg/d) vs placebo at 24 weeks							
Burns 1999	205	2.49 (41.24)	214	5.22 (41.4)		55.6 %	-2.73 [-10.64, 5.18]
Rogers 1998b	131	8.11 (36.4)	131	-0.4 (36.74)		44.4 %	8.51 [-0.35, 17.37]
Subtotal (95% CI)	**336**		**345**			**100.0 %**	**2.26 [-3.64, 8.16]**
Heterogeneity: Chi² = 3.44, df = 1 (P = 0.06); I² =71%							
Test for overall effect: Z = 0.75 (P = 0.45)							
3 donepezil (10 mg/d) vs placebo at 12 weeks							
Burns 1999	214	0.68 (37.01)	241	3.75 (37.1)		40.8 %	-3.07 [-9.89, 3.75]
Rogers 1998a	156	4.3 (33.6)	150	-4 (33.6)		33.5 %	8.30 [0.77, 15.83]
Rogers 1998b	122	0.27 (36.12)	137	1.34 (36.75)		24.0 %	-1.07 [-9.96, 7.82]
Study 205	6	1.75 (28.05)	5	8.1 (28.04)		1.7 %	-6.35 [-39.63, 26.93]
Subtotal (95% CI)	**498**		**533**			**100.0 %**	**1.16 [-3.20, 5.52]**
Heterogeneity: Chi² = 5.37, df = 3 (P = 0.15); I² =44%							
Test for overall effect: Z = 0.52 (P = 0.60)							
4 donepezil (10 mg/d) vs placebo at 24 weeks							
Burns 1999	196	2.77 (41.02)	214	5.22 (41.4)		58.1 %	-2.45 [-10.43, 5.53]
Rogers 1998b	104	0.2 (36.41)	131	-0.4 (36.74)		41.9 %	0.60 [-8.81, 10.01]
Subtotal (95% CI)	**300**		**345**			**100.0 %**	**-1.17 [-7.26, 4.91]**
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² =0.0%							
Test for overall effect: Z = 0.38 (P = 0.71)							

Analysis 2.21. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 21 QoL (participant-rated quality of life) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 21 QoL (participant-rated quality of life) ITT-LOCF

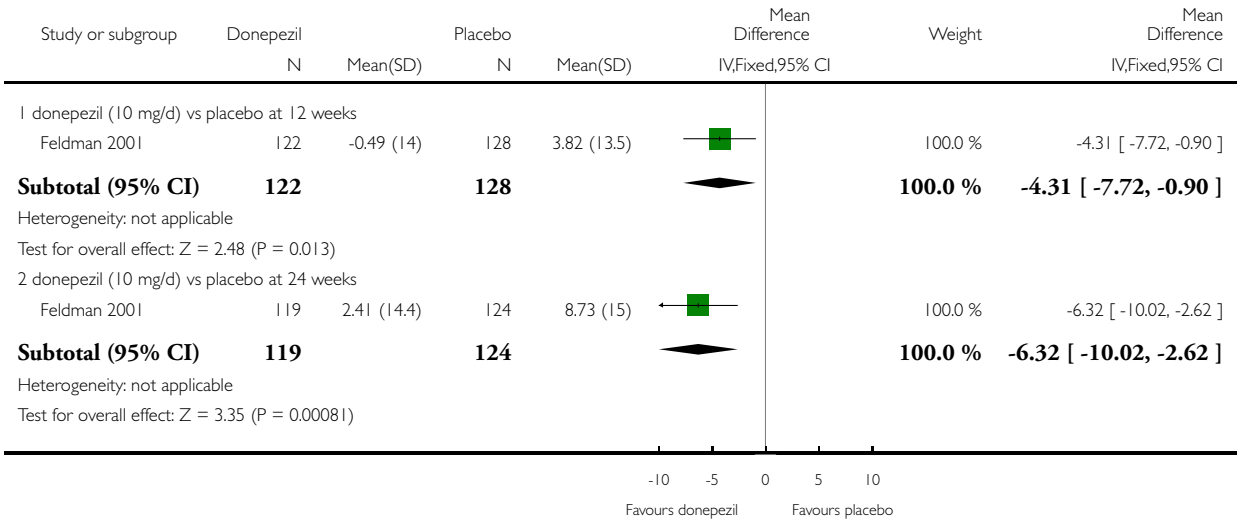


Analysis 2.22. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 22 IADL (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 22 IADL (change from baseline) completers

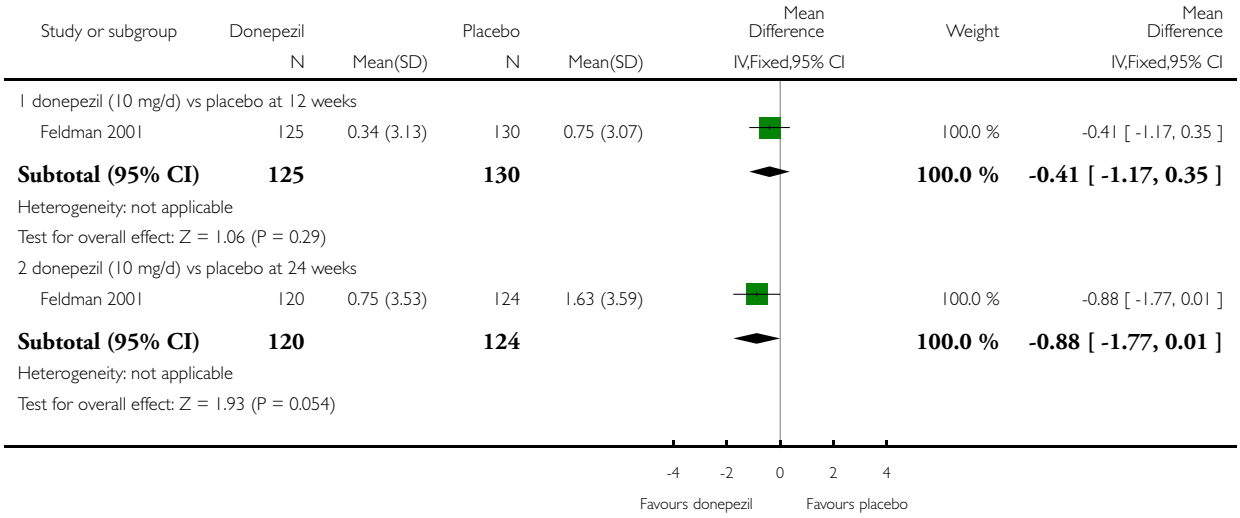


Analysis 2.23. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 23 PSMS (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 23 PSMS (change from baseline) completers

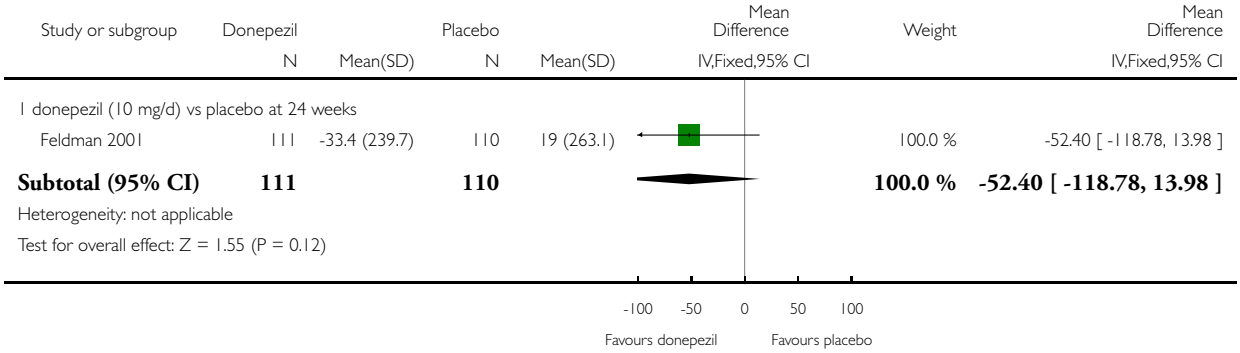


Analysis 2.24. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 24 Time (mins/day) spent by carer assisting in IADL and PSMS (change from baseline) LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 24 Time (mins/day) spent by carer assisting in IADL and PSMS (change from baseline) LOCF

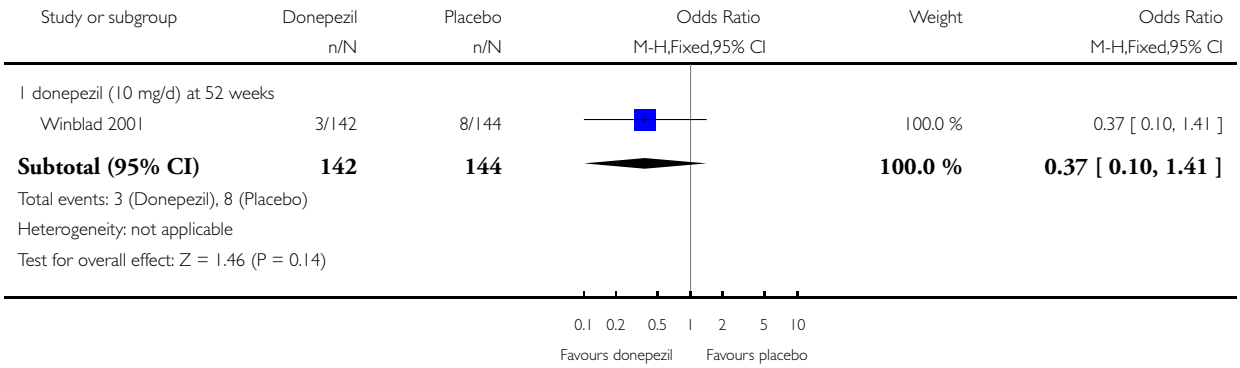


Analysis 2.25. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 25 Total number who enter long-term institutional care before end of treatment.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 25 Total number who enter long-term institutional care before end of treatment

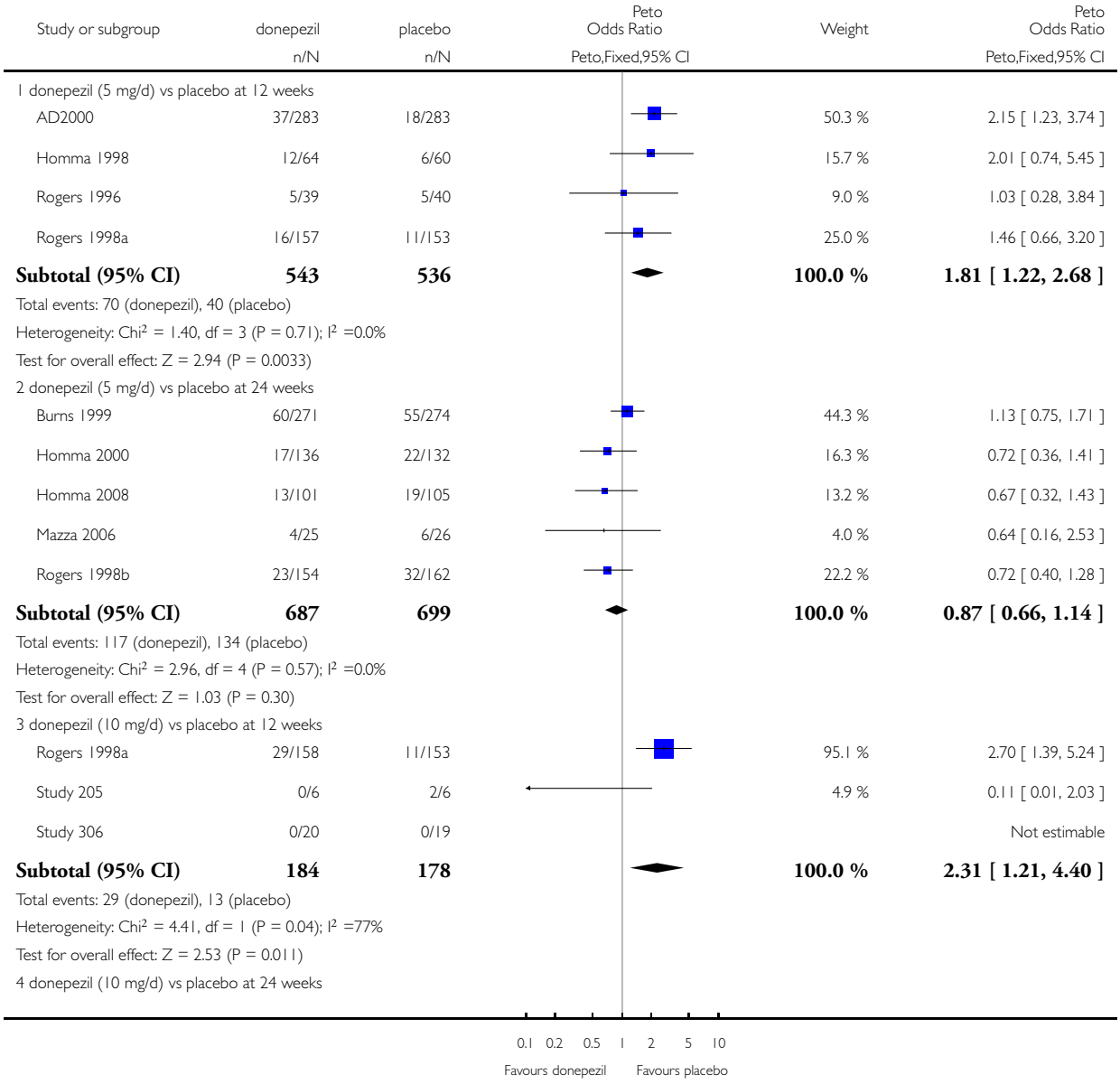


Analysis 2.26. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 26 Total number of withdrawals before end of treatment.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 26 Total number of withdrawals before end of treatment



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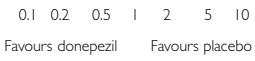
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Black 2007	59/176	40/167		14.5 %	1.59 [1.00, 2.54]
Burns 1999	72/273	55/274		20.1 %	1.42 [0.96, 2.12]
Feldman 2001	23/144	20/147		7.6 %	1.21 [0.63, 2.30]
Homma 2008	20/96	19/105		6.5 %	1.19 [0.59, 2.39]
Jia 2017	29/157	30/156		9.9 %	0.95 [0.54, 1.68]
Krishnan 2003	6/34	10/33		2.5 %	0.50 [0.17, 1.54]
Maher-Edwards 2011	10/67	15/61		4.2 %	0.54 [0.23, 1.30]
Rogers 1998b	51/157	32/162		12.7 %	1.93 [1.17, 3.19]
Seltzer 2004	26/96	11/57		5.4 %	1.52 [0.71, 3.27]
Tariot 2001	19/103	27/105		7.4 %	0.66 [0.34, 1.26]
Tune 2003	0/14	2/14		0.4 %	0.13 [0.01, 2.11]
Winblad 2006	33/128	21/120		8.7 %	1.62 [0.89, 2.96]
Subtotal (95% CI)	**1445**	**1401**		**100.0 %**	**1.25 [1.05, 1.50]**
Total events: 348 (donepezil), 282 (placebo)					
Heterogeneity: Chi^2 = 18.61, df = 11 (P = 0.07); I^2 =41%					
Test for overall effect: Z = 2.49 (P = 0.013)					
5 donepezil (10 mg/d) vs placebo at 52 weeks					
Winblad 2001	47/142	47/144		100.0 %	1.02 [0.62, 1.67]
Subtotal (95% CI)	**142**	**144**		**100.0 %**	**1.02 [0.62, 1.67]**
Total events: 47 (donepezil), 47 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.93)					
Test for subgroup differences: Chi^2 = 14.12, df = 4 (P = 0.01), I^2 =72%					



Analysis 2.27. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 27 Total number of participants who withdrew due to an adverse event.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 27 Total number of participants who withdrew due to an adverse event

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks					
Homma 1998	7/64	2/60		36.8 %	3.07 [0.79, 11.85]
Rogers 1996	3/39	2/40		20.8 %	1.57 [0.26, 9.47]
Rogers 1998a	7/157	3/153		42.5 %	2.22 [0.63, 7.81]
Subtotal (95% CI)	**260**	**253**		**100.0 %**	**2.33 [1.02, 5.28]**
Total events: 17 (donepezil), 7 (placebo)					
Heterogeneity: Chi^2 = 0.35, df = 2 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 2.02 (P = 0.044)					
2 donepezil (5 mg/d) vs placebo at 24 weeks					
Burns 1999	24/271	27/274		51.3 %	0.89 [0.50, 1.58]
Homma 2000	2/136	6/132		8.6 %	0.35 [0.09, 1.41]
Homma 2008	8/101	11/105		19.2 %	0.74 [0.29, 1.89]
Rogers 1998b	9/154	11/162		20.8 %	0.85 [0.35, 2.11]
Subtotal (95% CI)	**662**	**673**		**100.0 %**	**0.78 [0.52, 1.18]**
Total events: 43 (donepezil), 55 (placebo)					
Heterogeneity: Chi^2 = 1.52, df = 3 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 1.15 (P = 0.25)					
3 donepezil (10 mg/d) vs placebo at 12 weeks					
Rogers 1998a	16/158	3/153		94.7 %	4.13 [1.64, 10.44]
Study 205	0/6	1/6		5.3 %	0.14 [0.00, 6.82]
Study 306	0/20	0/19			Not estimable
Subtotal (95% CI)	**184**	**178**		**100.0 %**	**3.45 [1.40, 8.50]**
Total events: 16 (donepezil), 4 (placebo)					
Heterogeneity: Chi^2 = 2.77, df = 1 (P = 0.10); I^2 =64%					
Test for overall effect: Z = 2.69 (P = 0.0071)					
4 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	34/176	18/167		15.8 %	1.94 [1.08, 3.50]
Burns 1999	50/273	27/274		23.7 %	2.01 [1.24, 3.25]
Feldman 2001	12/144	9/147		7.0 %	1.39 [0.57, 3.37]

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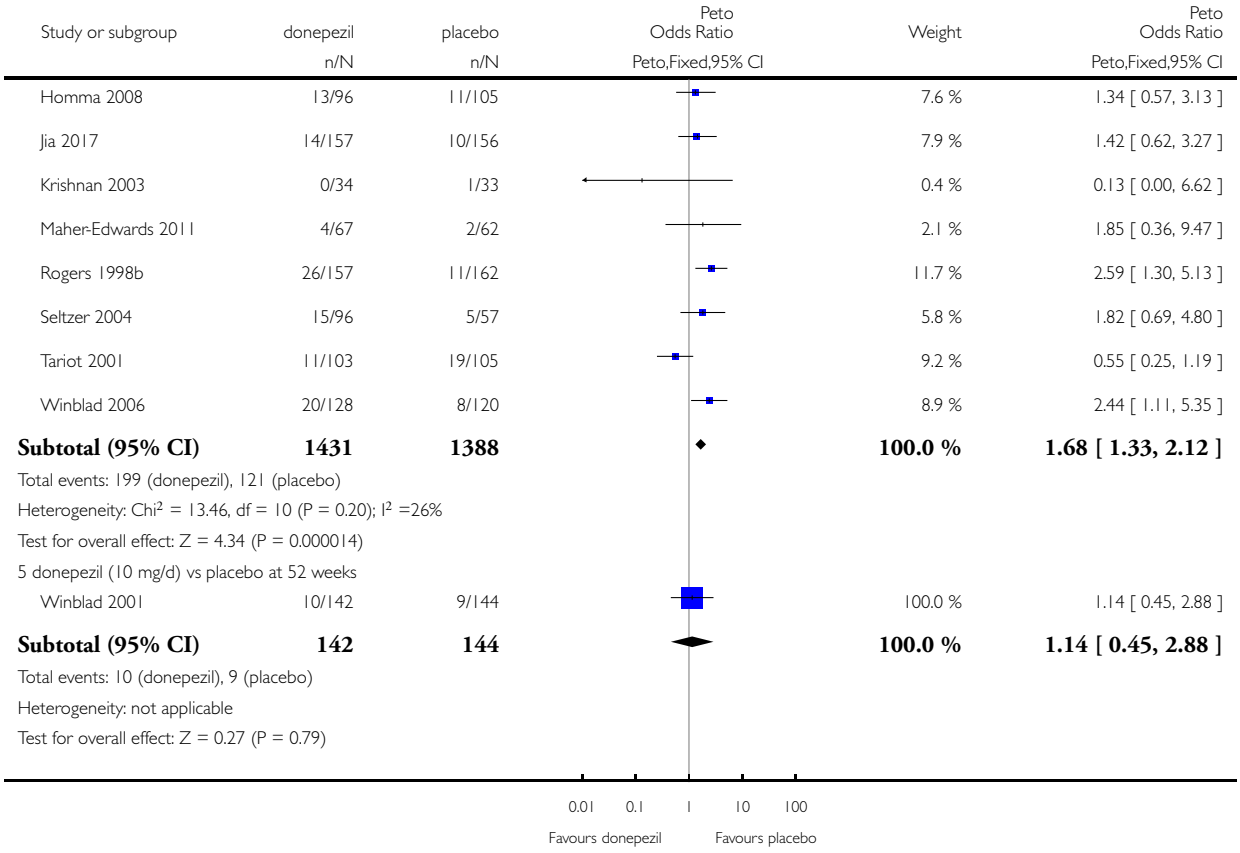


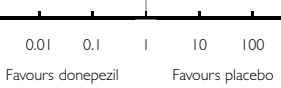
Analysis 2.28. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 28 Total number of participants who suffered from at least one adverse event.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 28 Total number of participants who suffered from at least one adverse event

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks					
Homma 1998	7/64	2/60		10.5 %	3.07 [0.79, 11.85]
Rogers 1996	3/39	2/40		5.9 %	1.57 [0.26, 9.47]
Rogers 1998a	106/157	106/153		83.6 %	0.92 [0.57, 1.49]
Subtotal (95% CI)	**260**	**253**		**100.0 %**	**1.08 [0.70, 1.67]**
Total events: 116 (donepezil), 110 (placebo)					
Heterogeneity: Chi^2 = 2.87, df = 2 (P = 0.24); I^2 =30%					
Test for overall effect: Z = 0.34 (P = 0.73)					
2 donepezil (5 mg/d) vs placebo at 24 weeks					
Burns 1999	213/271	207/274		49.9 %	1.19 [0.80, 1.77]
Homma 2000	54/136	33/131		30.4 %	1.93 [1.16, 3.22]
Homma 2008	79/101	77/105		19.7 %	1.30 [0.69, 2.46]
Subtotal (95% CI)	**508**	**510**		**100.0 %**	**1.40 [1.06, 1.86]**
Total events: 346 (donepezil), 317 (placebo)					
Heterogeneity: Chi^2 = 2.22, df = 2 (P = 0.33); I^2 =10%					
Test for overall effect: Z = 2.35 (P = 0.019)					
3 donepezil (10 mg/d) vs placebo at 12 weeks					
Rogers 1998a	124/158	106/153		98.4 %	1.61 [0.97, 2.67]
Study 205	0/6	1/6		1.6 %	0.14 [0.00, 6.82]
Subtotal (95% CI)	**164**	**159**		**100.0 %**	**1.55 [0.94, 2.55]**
Total events: 124 (donepezil), 107 (placebo)					
Heterogeneity: Chi^2 = 1.51, df = 1 (P = 0.22); I^2 =34%					
Test for overall effect: Z = 1.70 (P = 0.089)					
4 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	140/176	117/167		16.5 %	1.65 [1.02, 2.69]
Burns 1999	234/273	207/274		21.9 %	1.91 [1.25, 2.92]
Feldman 2001	120/144	117/147		11.3 %	1.28 [0.71, 2.31]
Homma 2008	80/96	77/105		8.8 %	1.79 [0.92, 3.49]
Jia 2017	42/157	26/156		13.6 %	1.81 [1.06, 3.09]



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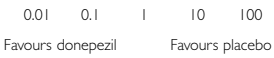
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Krishnan 2003	0/34	1/33		0.3 %	0.13 [0.00, 6.62]
Maher-Edwards 2011	26/67	18/62		7.4 %	1.54 [0.75, 3.18]
Seltzer 2004	67/96	37/57		8.0 %	1.25 [0.62, 2.52]
Tariot 2001	99/103	102/105		1.7 %	0.73 [0.16, 3.29]
Winblad 2006	105/128	91/120		10.5 %	1.45 [0.79, 2.67]
Subtotal (95% CI)	**1274**	**1226**		**100.0 %**	**1.59 [1.30, 1.94]**
Total events: 913 (donepezil), 793 (placebo)					
Heterogeneity: Chi^2 = 4.75, df = 9 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 4.58 (P < 0.00001)					
5 donepezil (10 mg/d) vs placebo at 52 weeks					
Winblad 2001	116/142	109/144		100.0 %	1.43 [0.81, 2.51]
Subtotal (95% CI)	**142**	**144**		**100.0 %**	**1.43 [0.81, 2.51]**
Total events: 116 (donepezil), 109 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.22)					

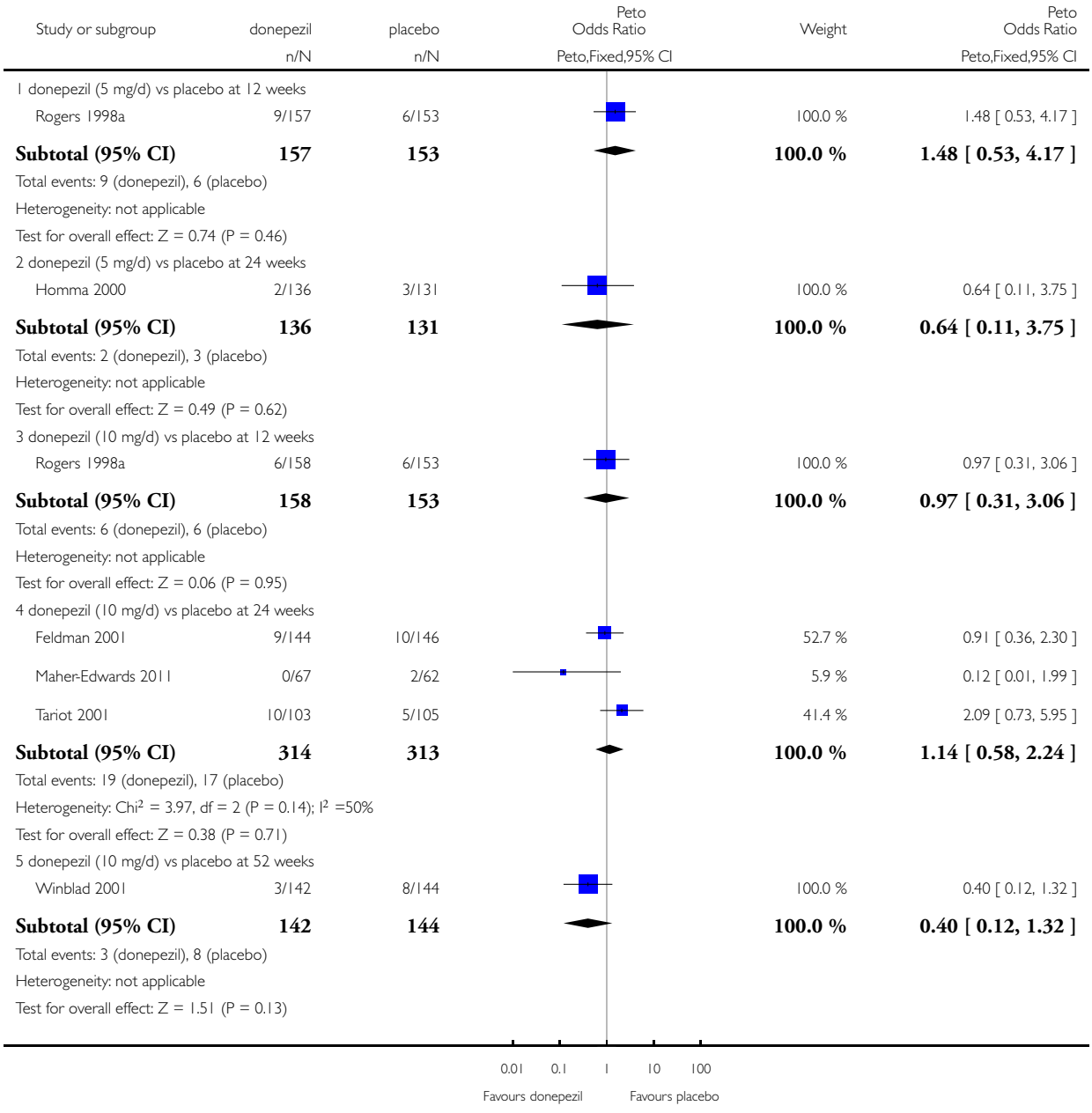


Analysis 2.29. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 29 Total number of participants who suffered from abdominal pain.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 29 Total number of participants who suffered from abdominal pain



Analysis 2.30. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 30 Total number of participants who suffered from abnormal gait.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 30 Total number of participants who suffered from abnormal gait

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks					
Tariot 2001	12/103	8/105		100.0 %	1.59 [0.63, 3.98]
Subtotal (95% CI)	**103**	**105**		**100.0 %**	**1.59 [0.63, 3.98]**
Total events: 12 (donepezil), 8 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					

Analysis 2.31. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 31 Total number of participants who suffered from abnormal dreams.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 31 Total number of participants who suffered from abnormal dreams

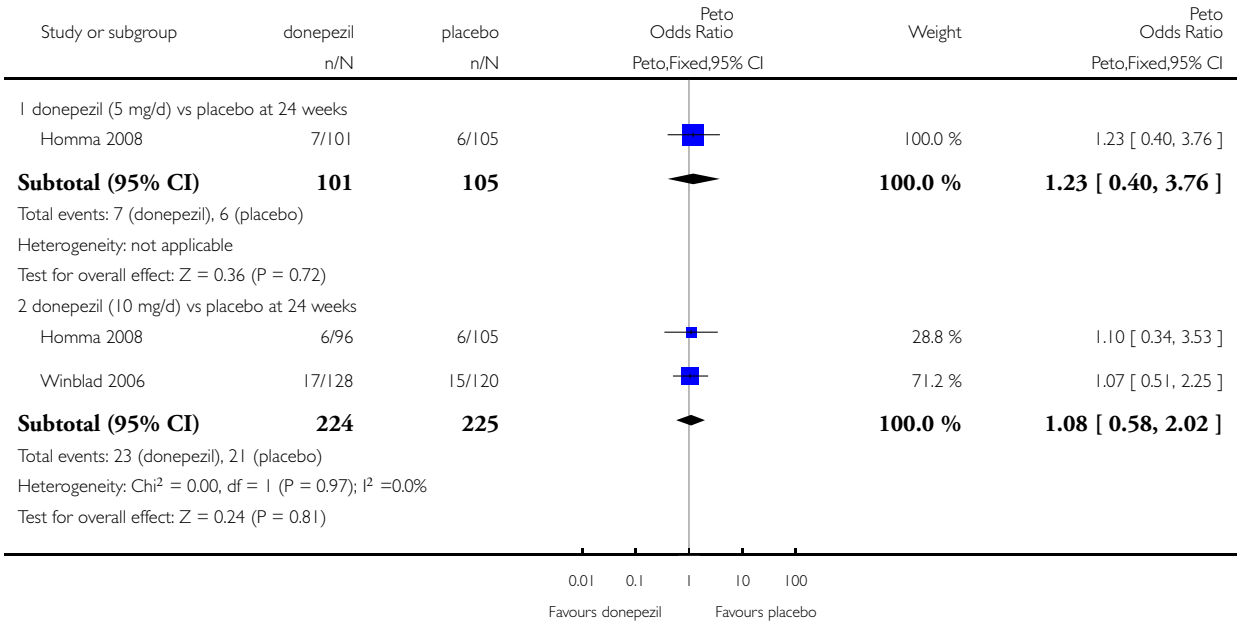
Study or subgroup	Donepezil n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 donepezil (10 mg/d) at 24 weeks					
Seltzer 2004	9/96	0/57		100.0 %	12.49 [0.71, 218.72]
Subtotal (95% CI)	**96**	**57**		**100.0 %**	**12.49 [0.71, 218.72]**
Total events: 9 (Donepezil), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.73 (P = 0.084)					

Analysis 2.32. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 32 Total number of participants who suffered from accidental fall.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 32 Total number of participants who suffered from accidental fall

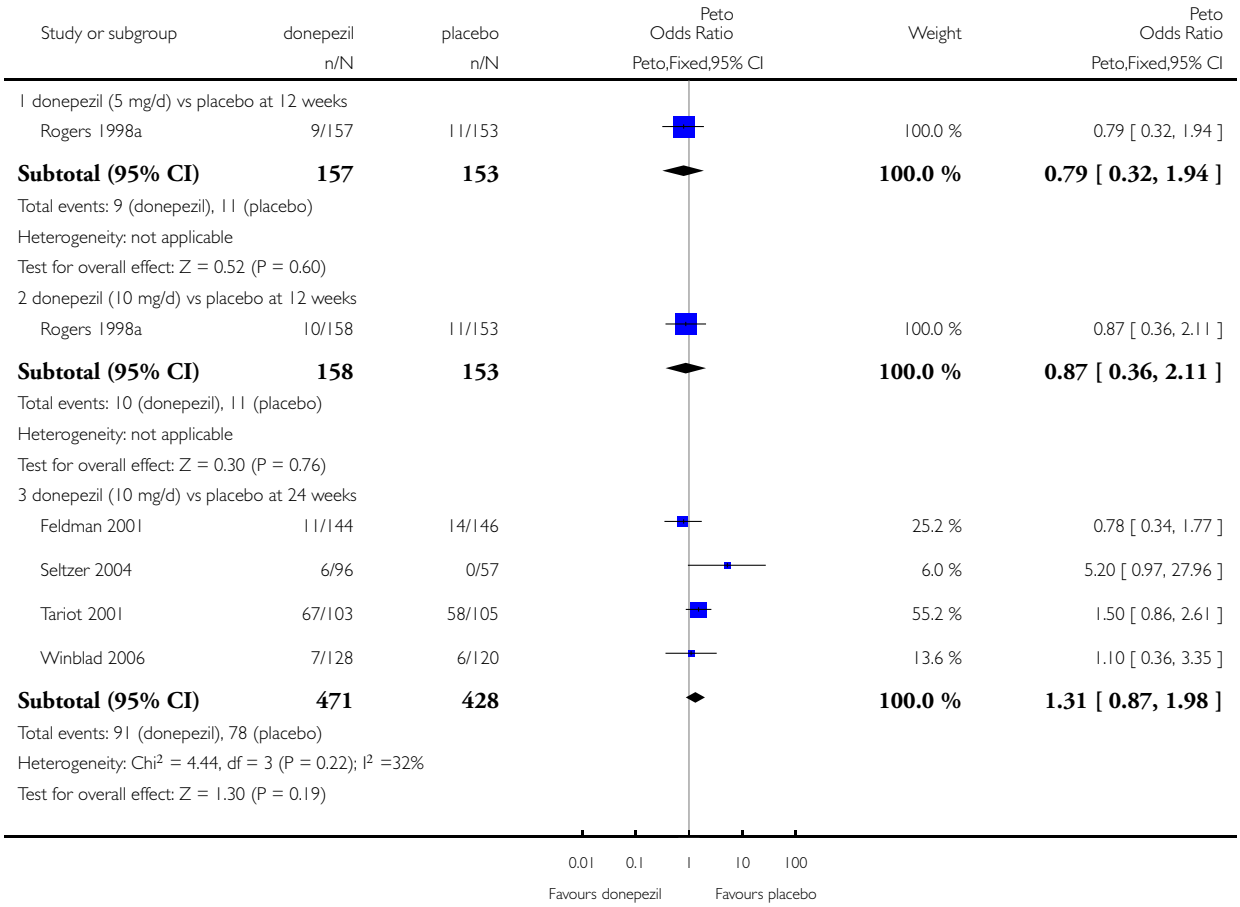


Analysis 2.33. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 33 Total number of participants who suffered from accidental injury.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 33 Total number of participants who suffered from accidental injury

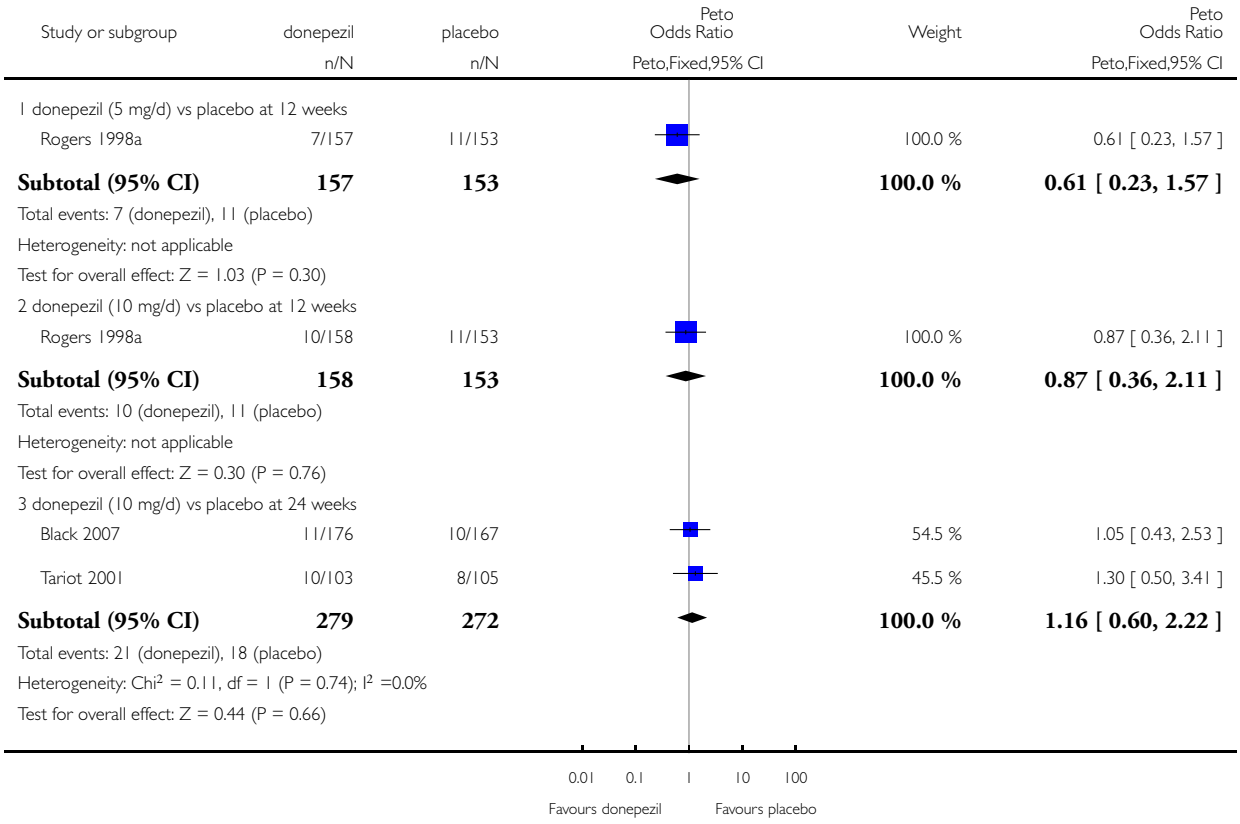


Analysis 2.34. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 34 Total number of participants who suffered from agitation.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 34 Total number of participants who suffered from agitation

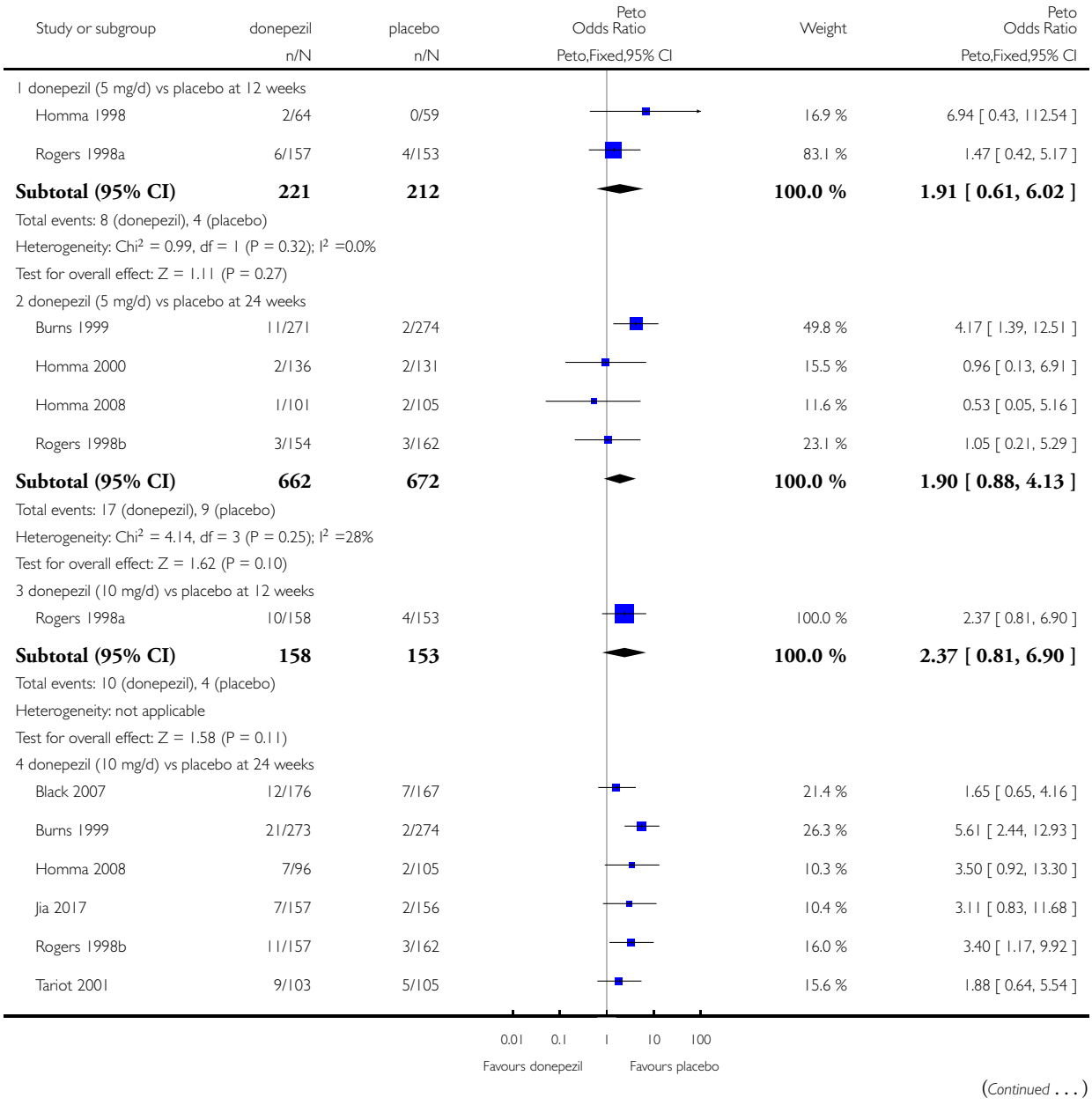


Analysis 2.35. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 35 Total number of participants who suffered from anorexia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 35 Total number of participants who suffered from anorexia



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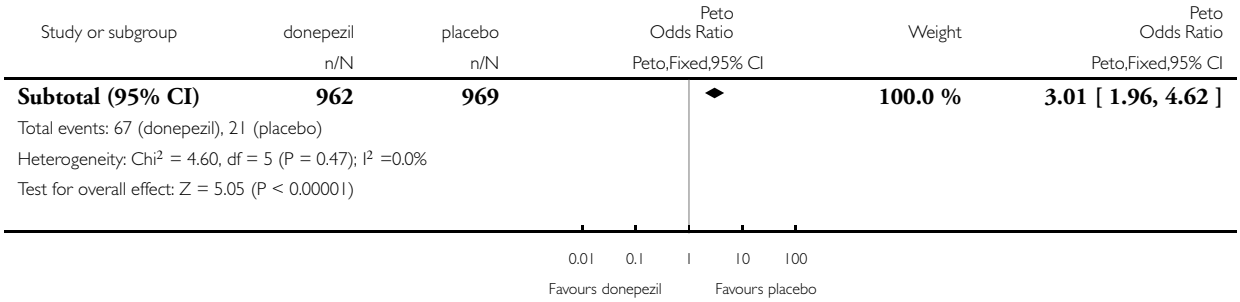
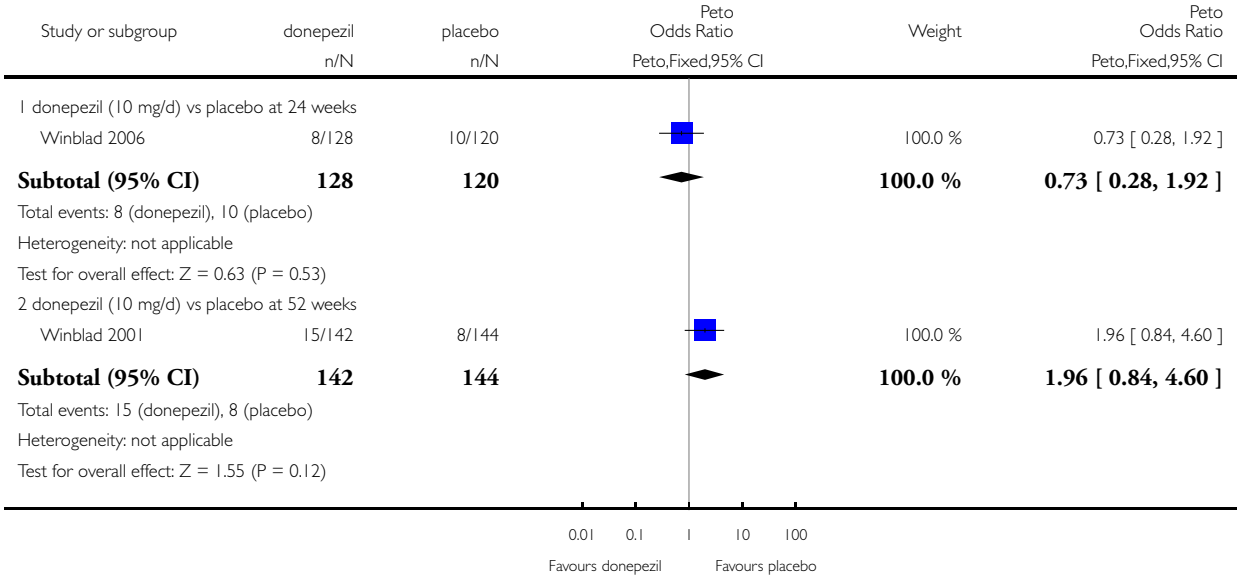


Analysis 2.36. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 36 Total number of participants who suffered from anxiety.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 36 Total number of participants who suffered from anxiety

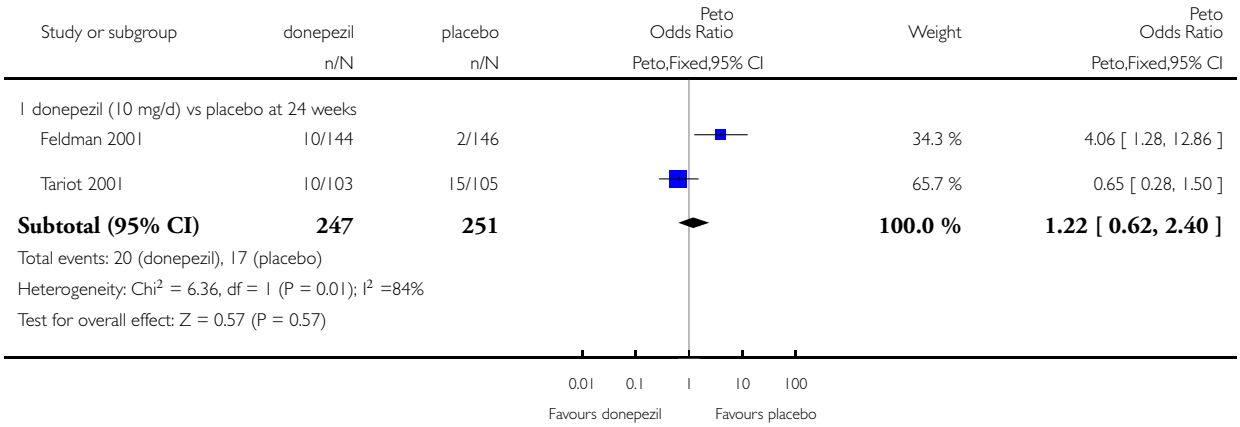


Analysis 2.37. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 37 Total number of participants who suffered from arthralgia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 37 Total number of participants who suffered from arthralgia

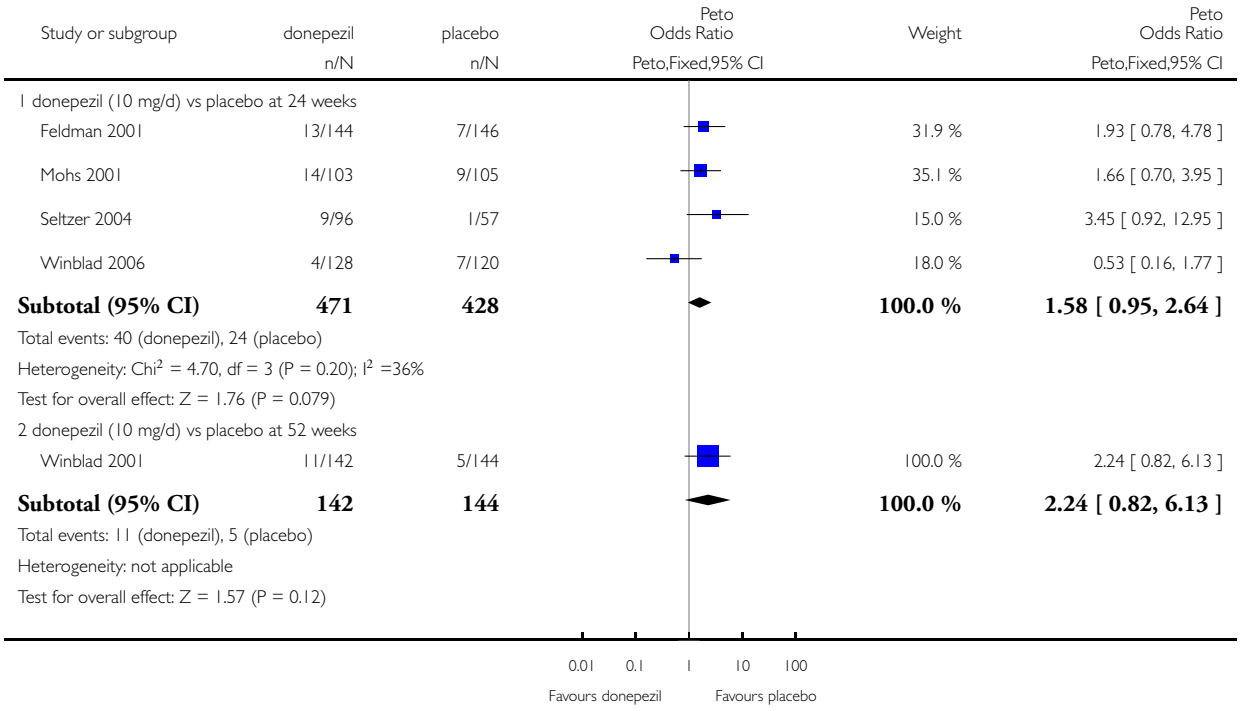


Analysis 2.38. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 38 Total number of participants who suffered from asthenia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 38 Total number of participants who suffered from asthenia

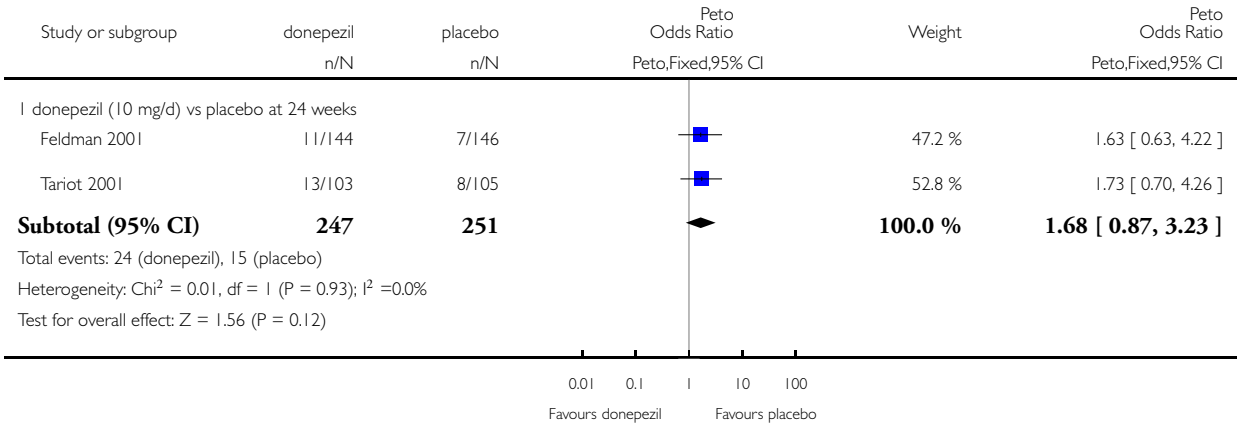


Analysis 2.39. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 39 Total number of participants who suffered from back pain.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 39 Total number of participants who suffered from back pain

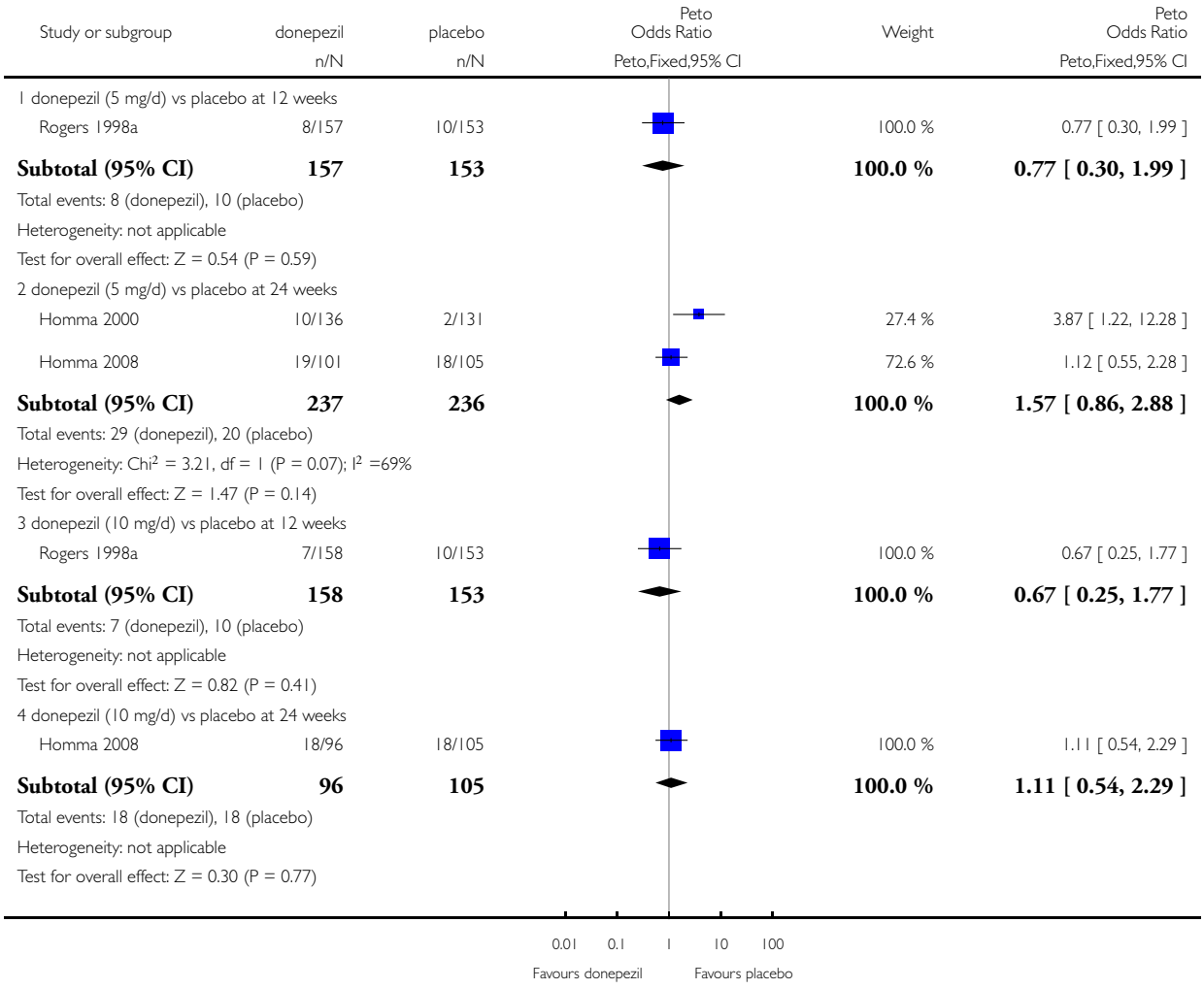


Analysis 2.40. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 40 Total number of participants who suffered from cold syndrome.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 40 Total number of participants who suffered from cold syndrome

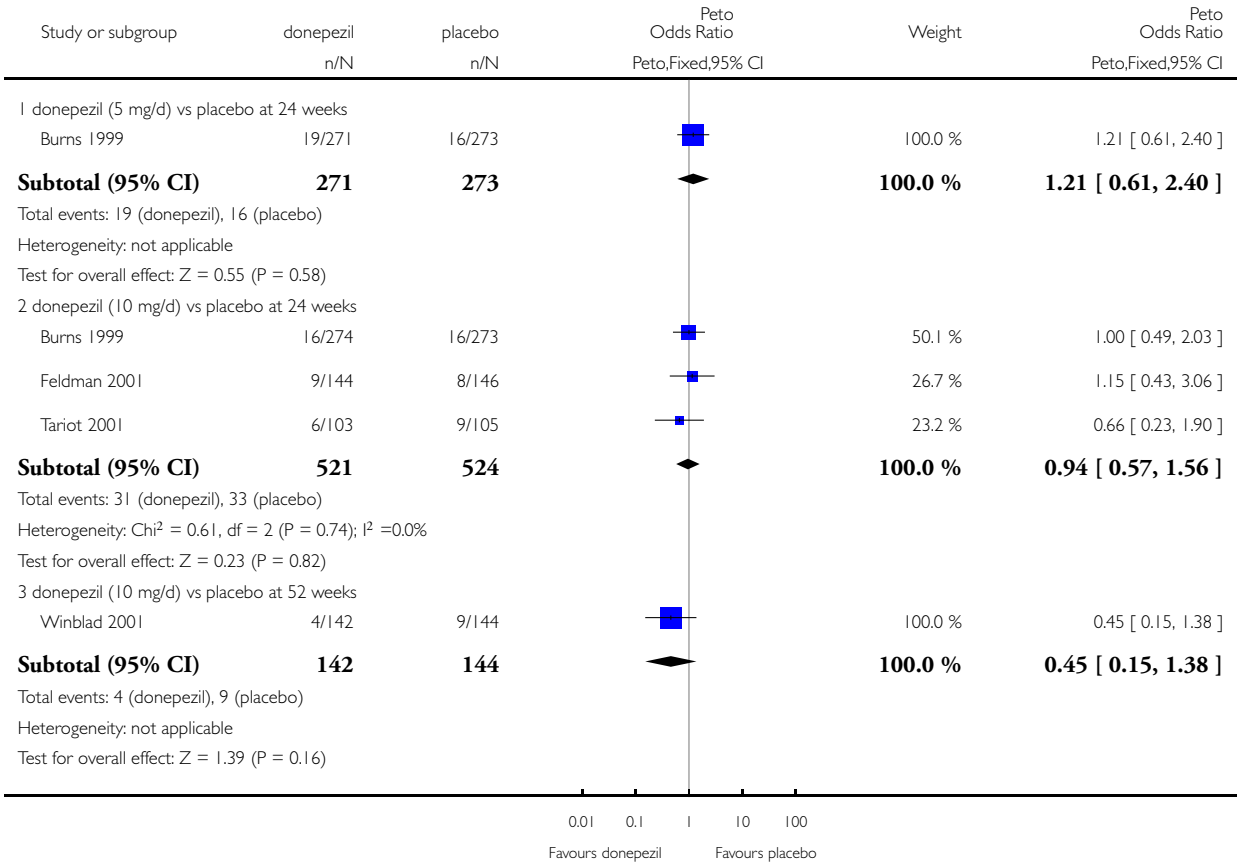


Analysis 2.41. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 41 Total number of participants who suffered from confusion.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 41 Total number of participants who suffered from confusion

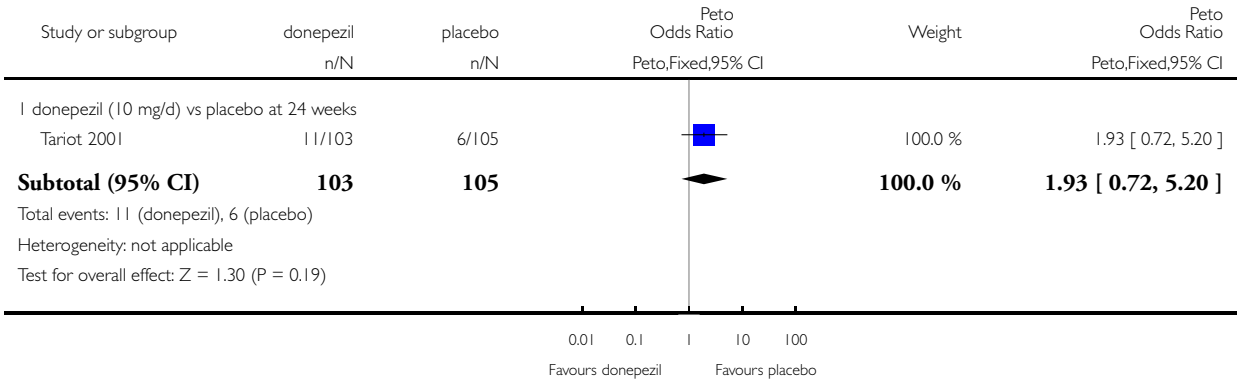


Analysis 2.42. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 42 Total number of participants who suffered from conjunctivitis.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 42 Total number of participants who suffered from conjunctivitis



Analysis 2.43. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 43 Total number of participants who suffered from constipation.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 43 Total number of participants who suffered from constipation

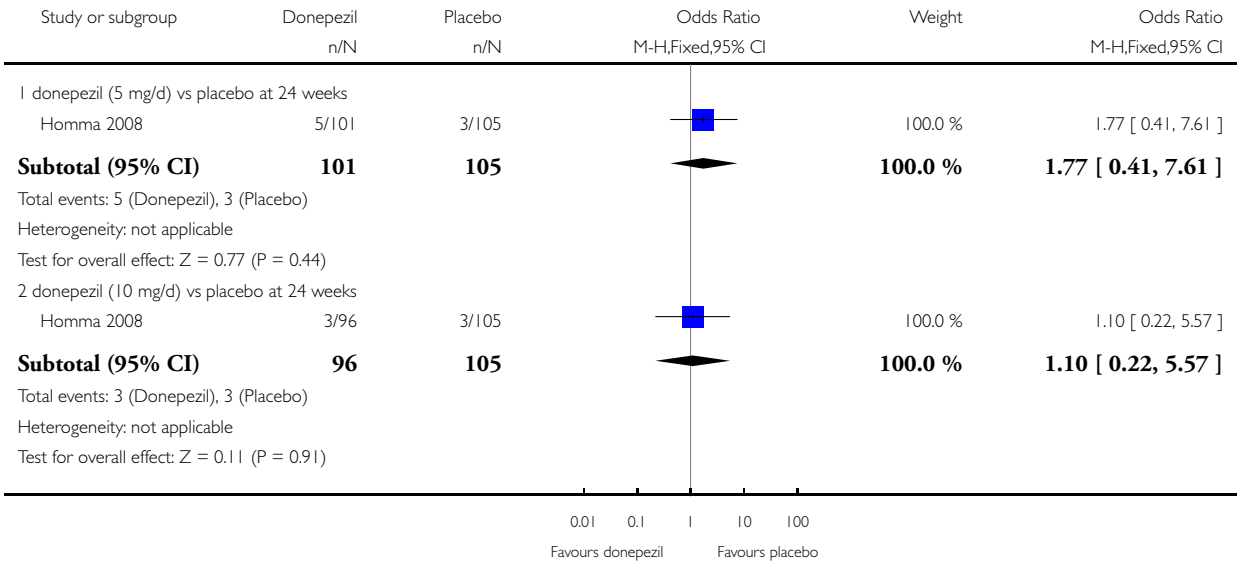
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 24 weeks					
Homma 2000	2/136	1/131		20.8 %	1.89 [0.19, 18.29]
Homma 2008	8/101	4/105		79.2 %	2.11 [0.66, 6.75]
Subtotal (95% CI)	**237**	**236**		**100.0 %**	**2.06 [0.73, 5.80]**
Total events: 10 (donepezil), 5 (placebo)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 1.37 (P = 0.17)					
2 donepezil (10 mg/d) vs placebo at 24 weeks					
Homma 2008	5/96	4/105		45.0 %	1.38 [0.36, 5.26]
Winblad 2006	5/128	6/120		55.0 %	0.77 [0.23, 2.59]
Subtotal (95% CI)	**224**	**225**		**100.0 %**	**1.01 [0.41, 2.46]**
Total events: 10 (donepezil), 10 (placebo)					
Heterogeneity: Chi^2 = 0.40, df = 1 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 0.01 (P = 0.99)					
3 donepezil (10 mg/d) vs placebo at 52 weeks					
Winblad 2001	6/142	9/144		100.0 %	0.67 [0.24, 1.88]
Subtotal (95% CI)	**142**	**144**		**100.0 %**	**0.67 [0.24, 1.88]**
Total events: 6 (donepezil), 9 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.77 (P = 0.44)					

Analysis 2.44. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 44 Total number of participants who suffered from contusion.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 44 Total number of participants who suffered from contusion



Analysis 2.45. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 45 Total number of participants who suffered from cystitis.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 45 Total number of participants who suffered from cystitis

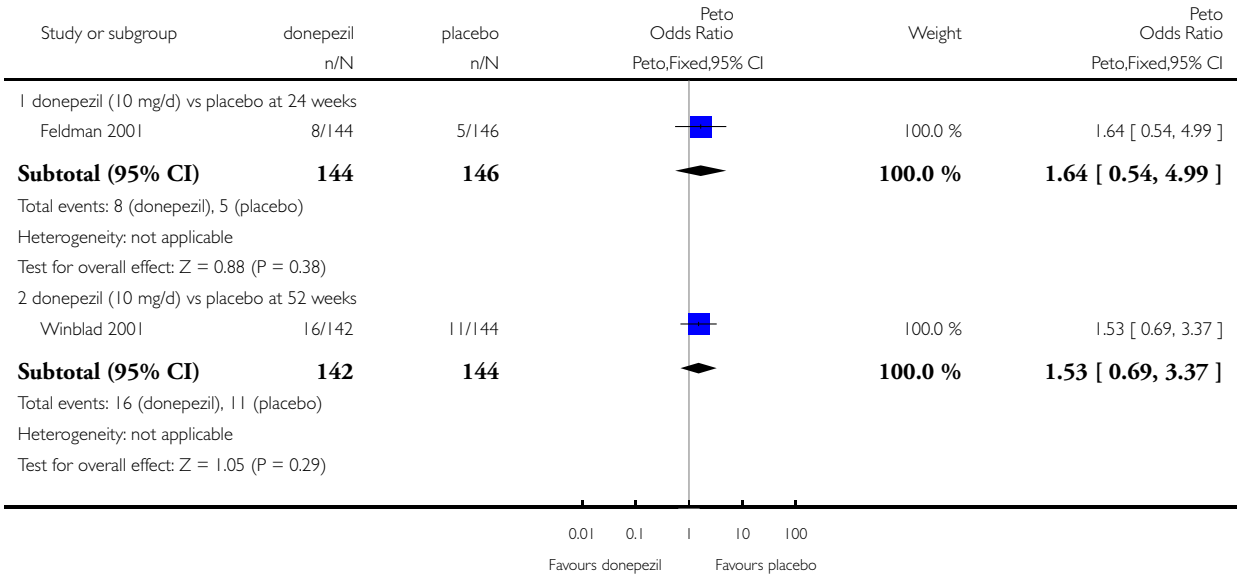
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks					
Winblad 2006	8/128	5/120		100.0 %	1.52 [0.50, 4.63]
Subtotal (95% CI)	**128**	**120**		**100.0 %**	**1.52 [0.50, 4.63]**
Total events: 8 (donepezil), 5 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.46)					

Analysis 2.46. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 46 Total number of participants who suffered from depression.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 46 Total number of participants who suffered from depression



Analysis 2.47. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 47 Total number of participants who suffered from diarrhoea.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 47 Total number of participants who suffered from diarrhoea

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks					
Rogers 1996	4/40	1/40		26.1 %	3.54 [0.59, 21.40]
Rogers 1998a	10/157	4/153		73.9 %	2.38 [0.82, 6.95]
Subtotal (95% CI)	**197**	**193**		**100.0 %**	**2.64 [1.05, 6.63]**
Total events: 14 (donepezil), 5 (placebo)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 2.07 (P = 0.038)					
2 donepezil (5 mg/d) vs placebo at 24 weeks					
Burns 1999	28/271	11/274		46.7 %	2.58 [1.35, 4.95]
Homma 2000	5/136	4/131		11.2 %	1.21 [0.32, 4.56]
Homma 2008	6/101	4/105		12.3 %	1.58 [0.45, 5.62]
Rogers 1998b	14/154	11/162		29.7 %	1.37 [0.61, 3.10]
Subtotal (95% CI)	**662**	**672**		**100.0 %**	**1.85 [1.19, 2.89]**
Total events: 53 (donepezil), 30 (placebo)					
Heterogeneity: Chi^2 = 1.98, df = 3 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 2.71 (P = 0.0067)					
3 donepezil (10 mg/d) vs placebo at 12 weeks					
Rogers 1998a	21/158	4/153		100.0 %	4.22 [1.87, 9.54]
Subtotal (95% CI)	**158**	**153**		**100.0 %**	**4.22 [1.87, 9.54]**
Total events: 21 (donepezil), 4 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.46 (P = 0.00055)					
4 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	18/176	7/167		11.5 %	2.44 [1.08, 5.50]
Burns 1999	45/273	11/274		24.9 %	3.87 [2.23, 6.73]
Feldman 2001	18/144	7/146		11.3 %	2.65 [1.17, 6.01]
Homma 2008	8/96	4/105		5.6 %	2.23 [0.70, 7.15]
Jia 2017	4/157	2/156		2.9 %	1.96 [0.39, 9.82]
Rogers 1998b	27/157	11/162		16.6 %	2.69 [1.37, 5.29]

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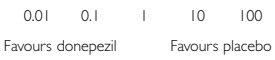
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Seltzer 2004	19/96	5/57		9.4 %	2.29 [0.93, 5.62]
Tariot 2001	15/103	10/105		10.9 %	1.61 [0.70, 3.70]
Winblad 2006	12/128	3/120		7.0 %	3.34 [1.18, 9.46]
Subtotal (95% CI)	**1330**	**1292**		**100.0 %**	**2.69 [2.05, 3.55]**
Total events: 166 (donepezil), 60 (placebo)					
Heterogeneity: Chi^2 = 3.74, df = 8 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 7.05 (P < 0.00001)					
5 donepezil (10 mg/d) vs placebo at 52 weeks					
Winblad 2001	10/142	10/144		100.0 %	1.02 [0.41, 2.52]
Subtotal (95% CI)	**142**	**144**		**100.0 %**	**1.02 [0.41, 2.52]**
Total events: 10 (donepezil), 10 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.97)					

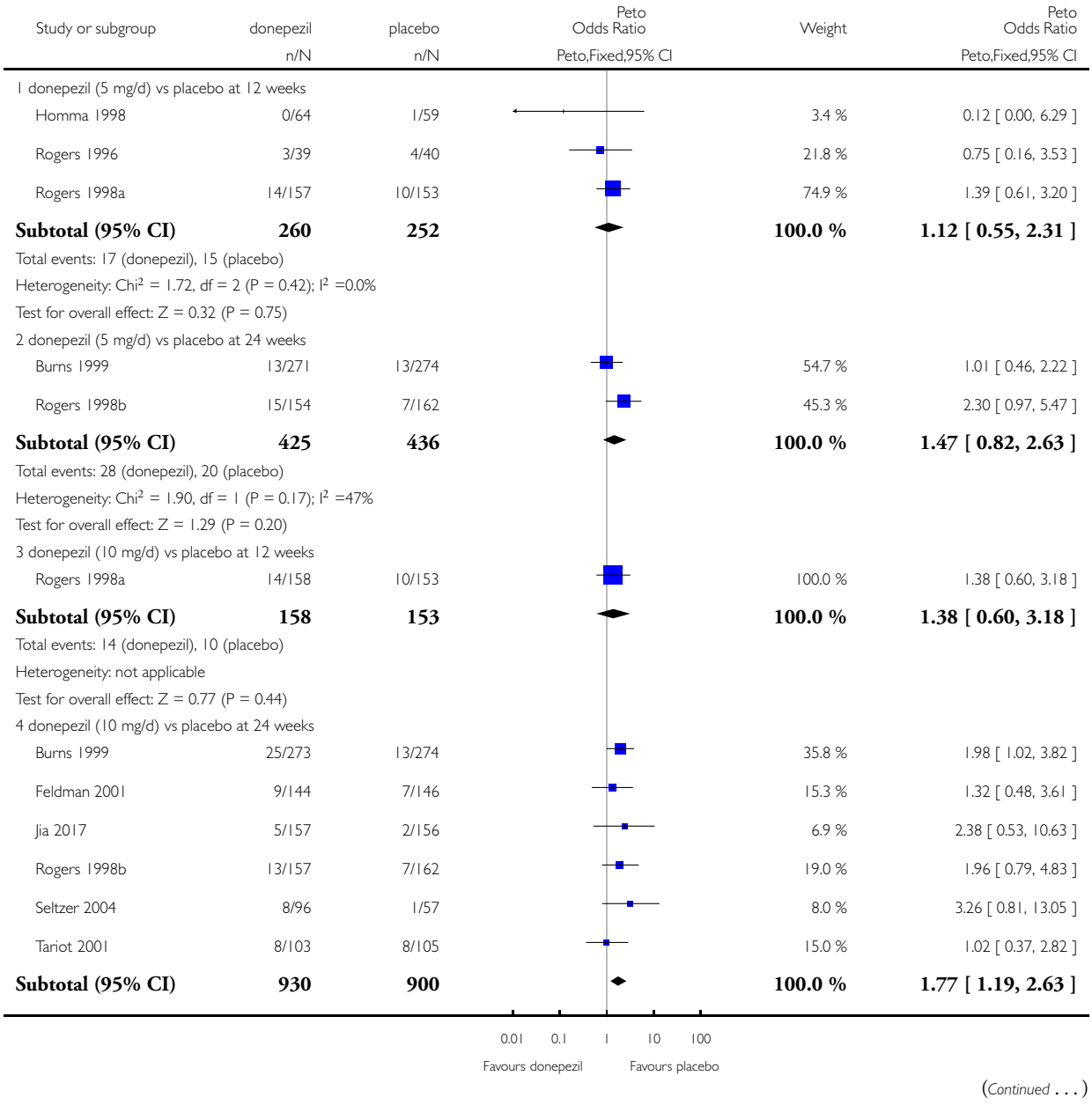


Analysis 2.48. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 48 Total number of participants who suffered from dizziness.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 48 Total number of participants who suffered from dizziness



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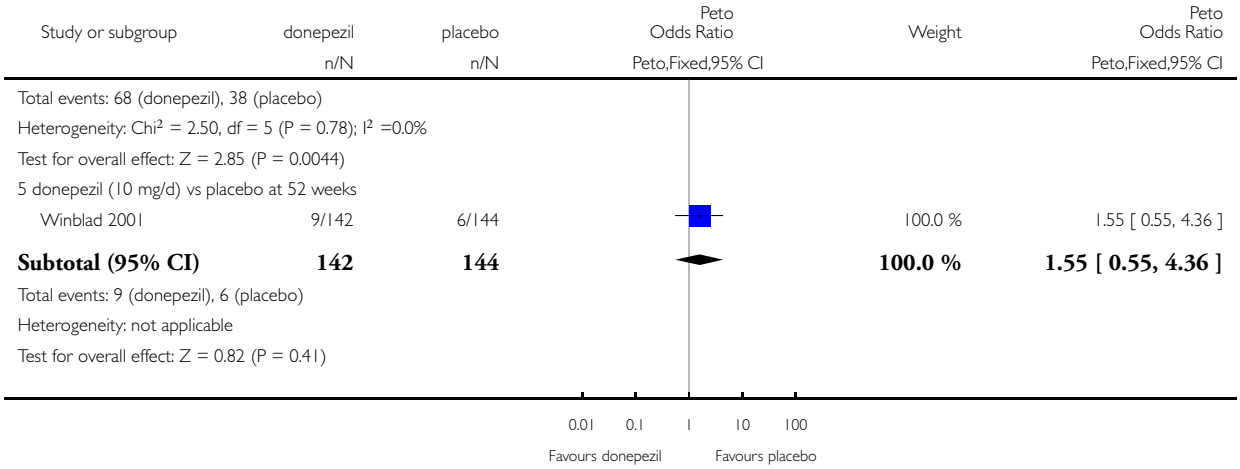
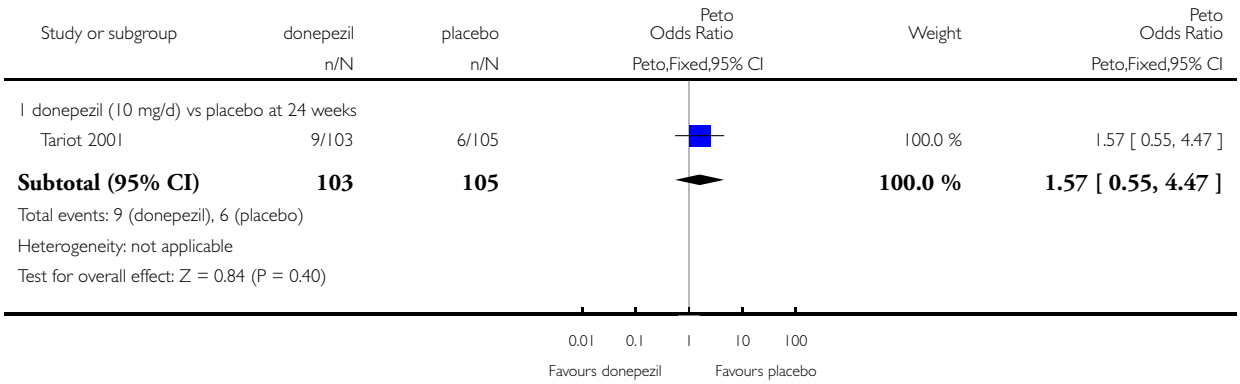


Analysis 2.49. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 49 Total number of participants who suffered from ecchymosis.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 49 Total number of participants who suffered from ecchymosis

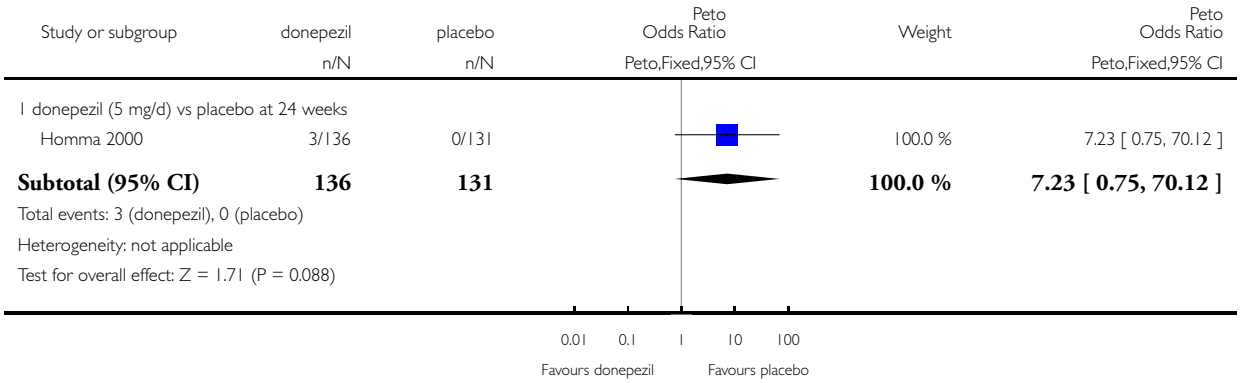


Analysis 2.50. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 50 Total number of participants who suffered from eczema.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 50 Total number of participants who suffered from eczema

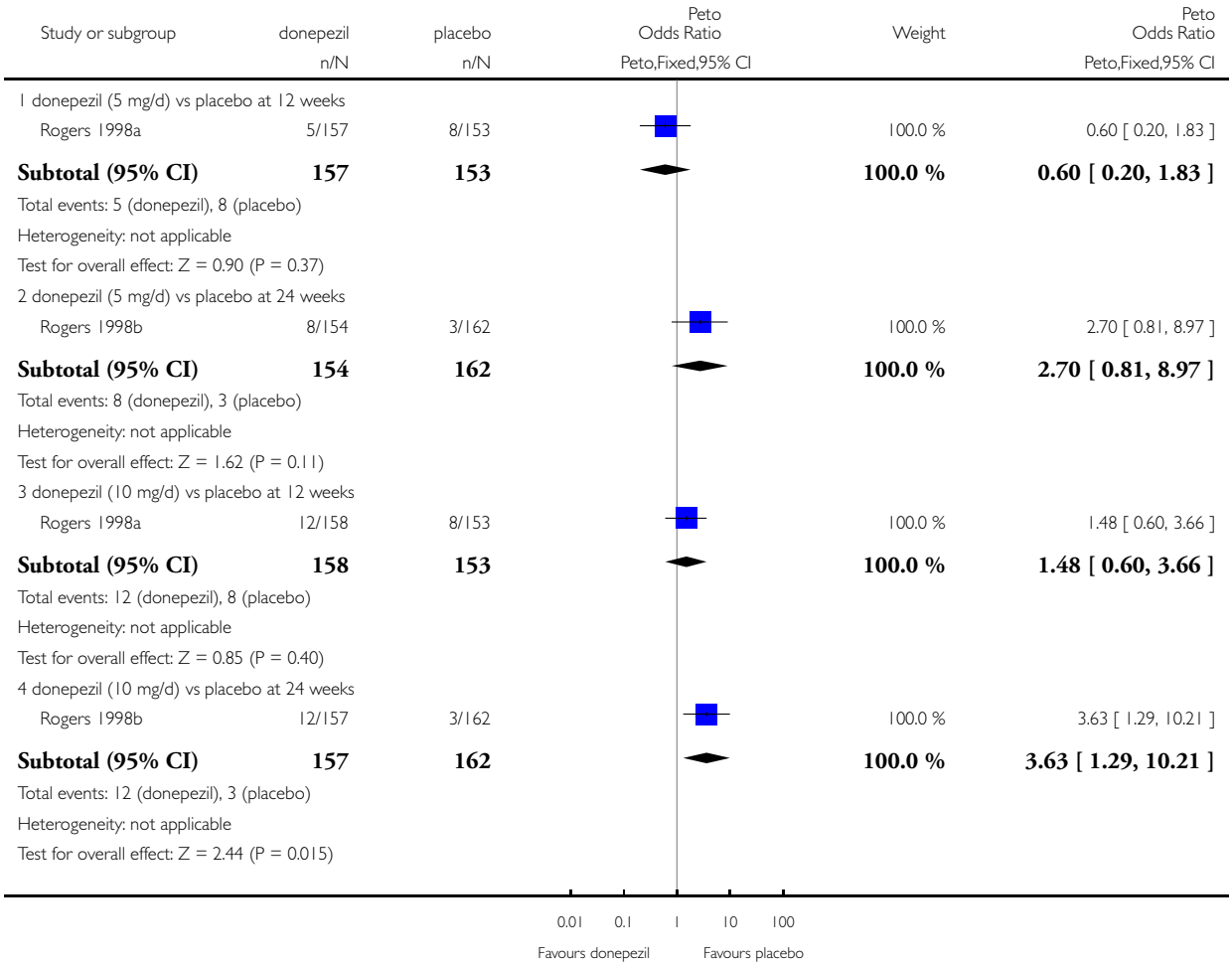


Analysis 2.51. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 51 Total number of participants who suffered from fatigue.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 51 Total number of participants who suffered from fatigue

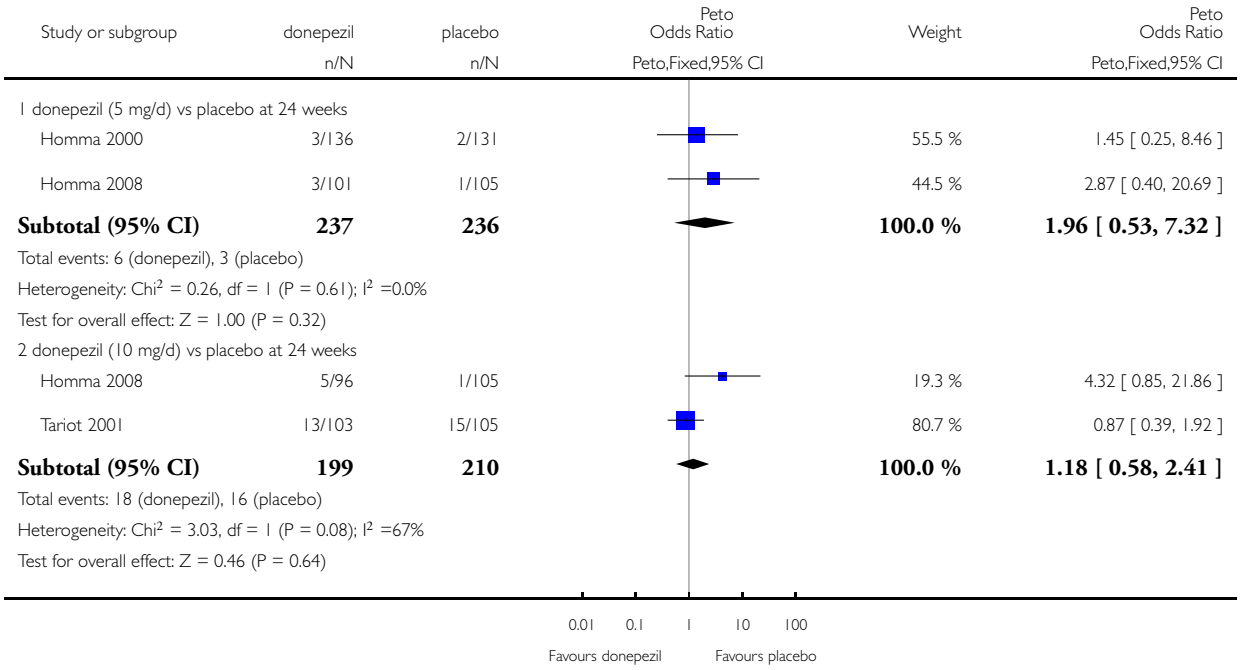


Analysis 2.52. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 52 Total number of participants who suffered from fever.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 52 Total number of participants who suffered from fever

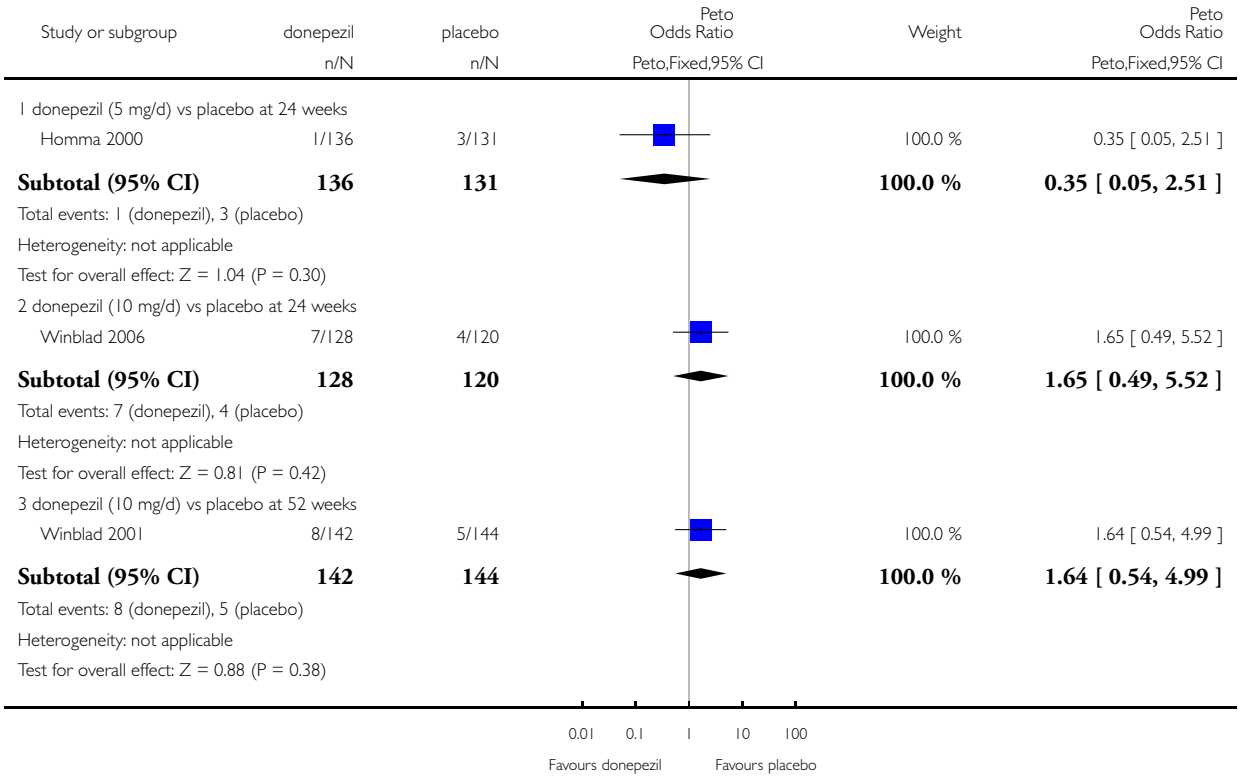


Analysis 2.53. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 53 Total number of participants who suffered from fracture.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 53 Total number of participants who suffered from fracture

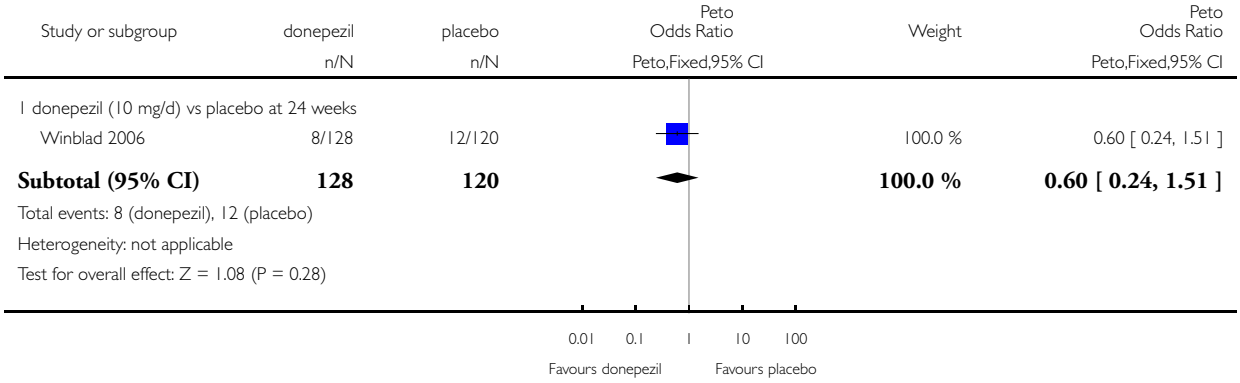


Analysis 2.54. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 54 Total number of participants who suffered from gastroenteritis.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 54 Total number of participants who suffered from gastroenteritis

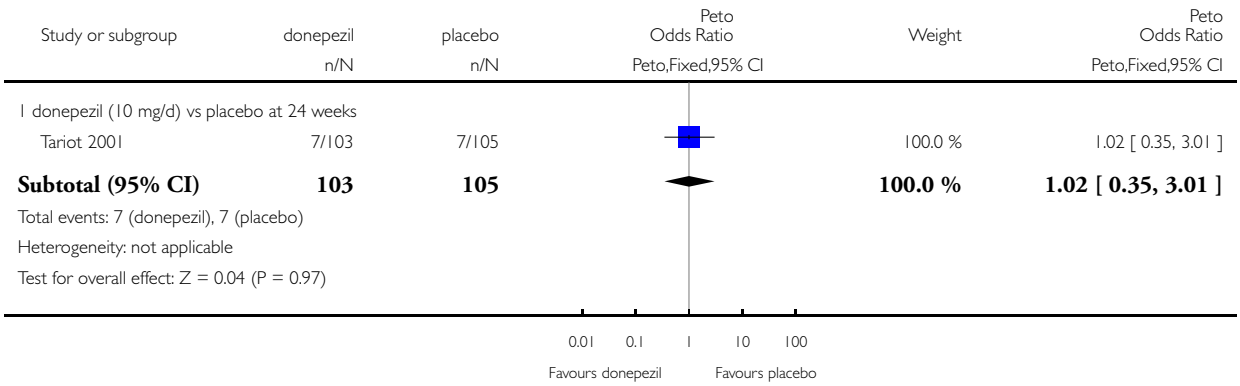


Analysis 2.55. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 55 Total number of participants who suffered from haemorrhage.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 55 Total number of participants who suffered from haemorrhage

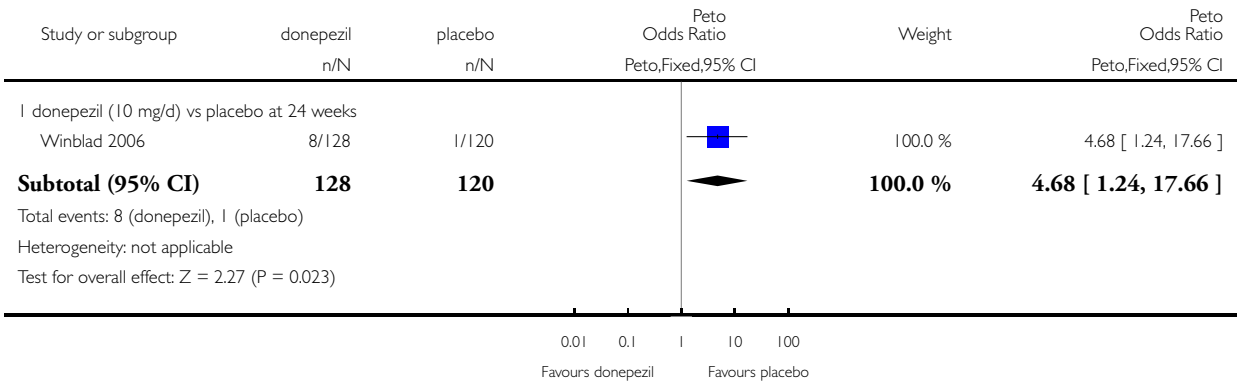


Analysis 2.56. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 56 Total number of participants who suffered from hallucinations.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 56 Total number of participants who suffered from hallucinations

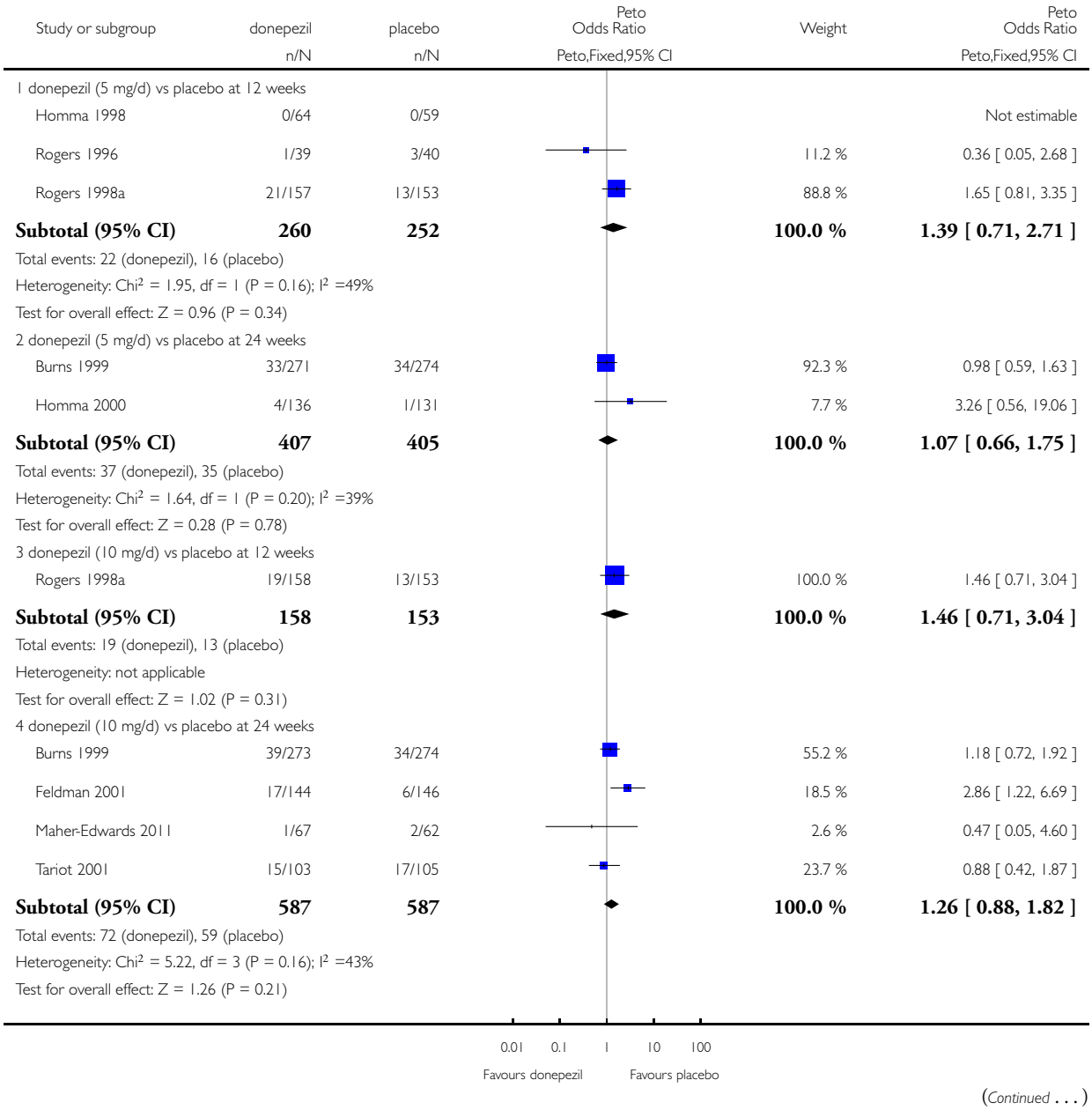


Analysis 2.57. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 57 Total number of participants who suffered from headache.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 57 Total number of participants who suffered from headache



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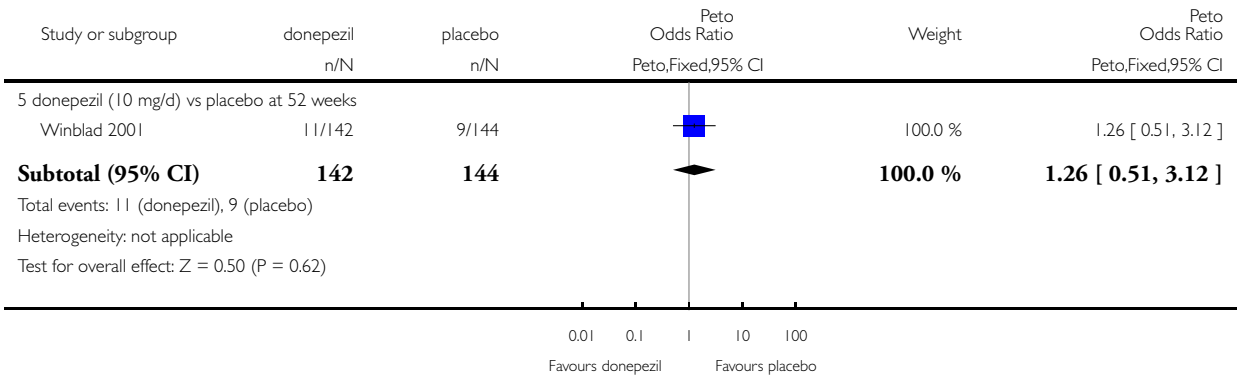
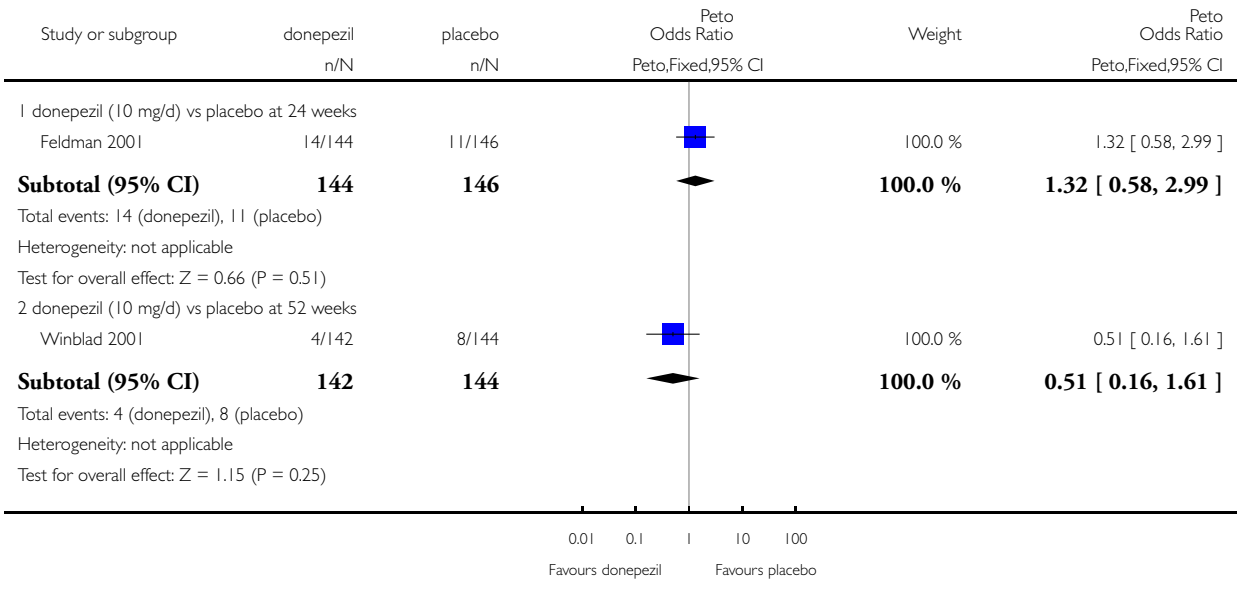


Analysis 2.58. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 58 Total number of participants who suffered from hostility.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 58 Total number of participants who suffered from hostility



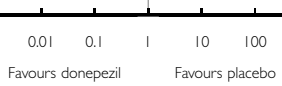
Analysis 2.59. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 59 Total number of participants who suffered from loss of appetite.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 59 Total number of participants who suffered from loss of appetite

Study or subgroup	Donepezil n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 24 weeks					
Homma 2008	5/101	2/105		100.0 %	2.68 [0.51, 14.15]
Subtotal (95% CI)	**101**	**105**		**100.0 %**	**2.68 [0.51, 14.15]**
Total events: 5 (Donepezil), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.24)					
2 donepezil (10 mg/d) vs placebo at 24 weeks					
Homma 2008	4/96	2/105		100.0 %	2.24 [0.40, 12.51]
Subtotal (95% CI)	**96**	**105**		**100.0 %**	**2.24 [0.40, 12.51]**
Total events: 4 (Donepezil), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					

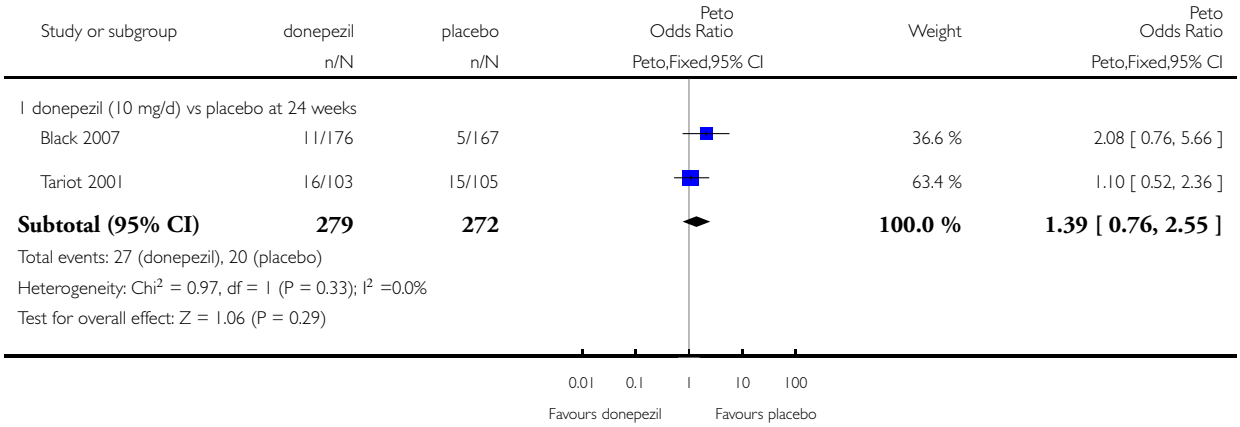


Analysis 2.60. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 60 Total number of participants who suffered from infection.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 60 Total number of participants who suffered from infection

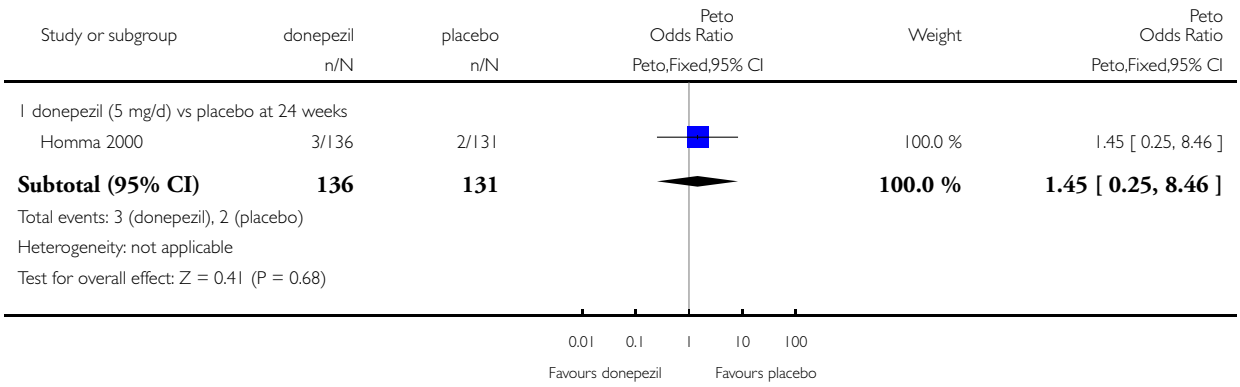


Analysis 2.61. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 61 Total number of participants who suffered from inflammation of upper airway.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 61 Total number of participants who suffered from inflammation of upper airway

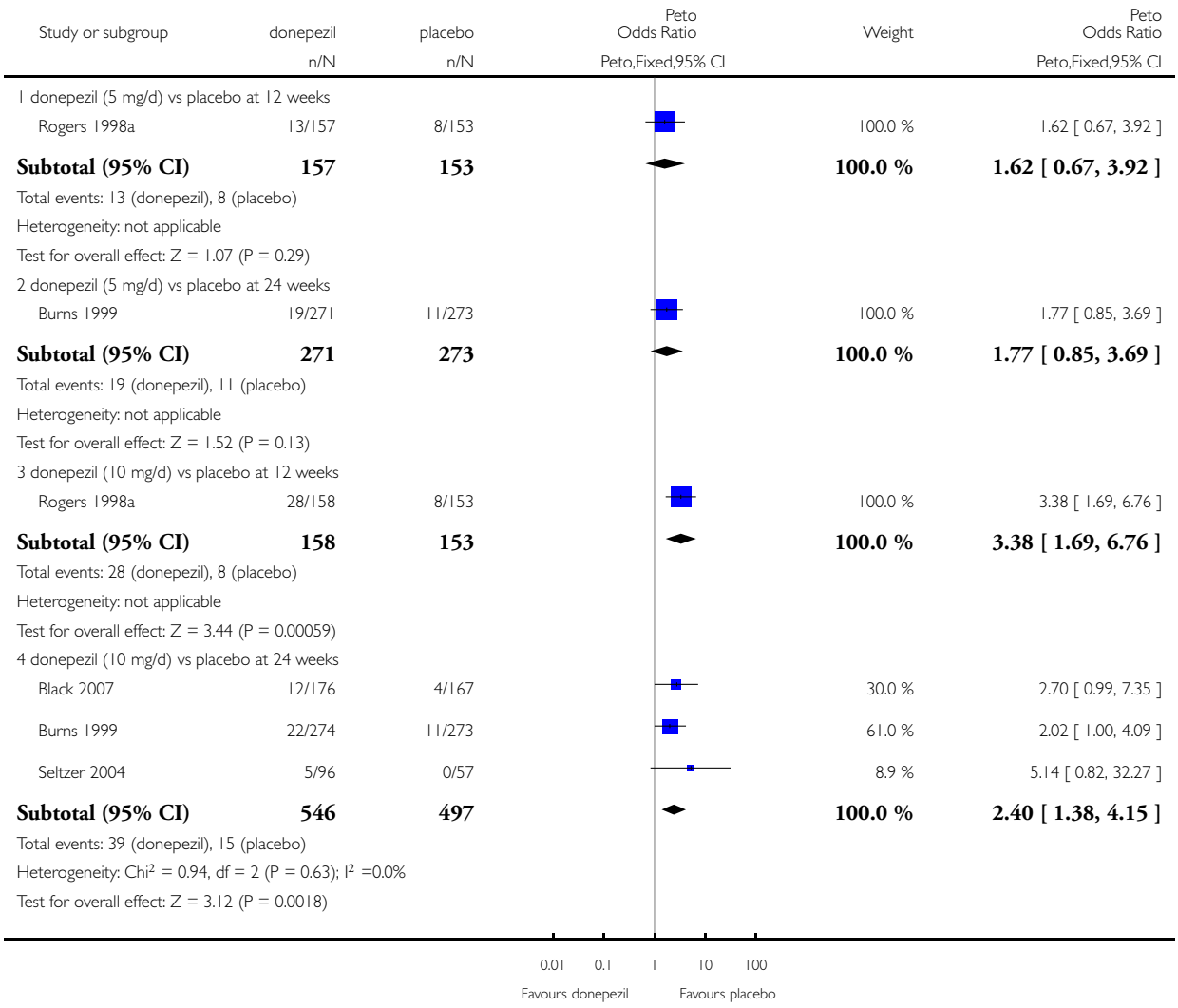


Analysis 2.62. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 62 Total number of participants who suffered from insomnia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 62 Total number of participants who suffered from insomnia



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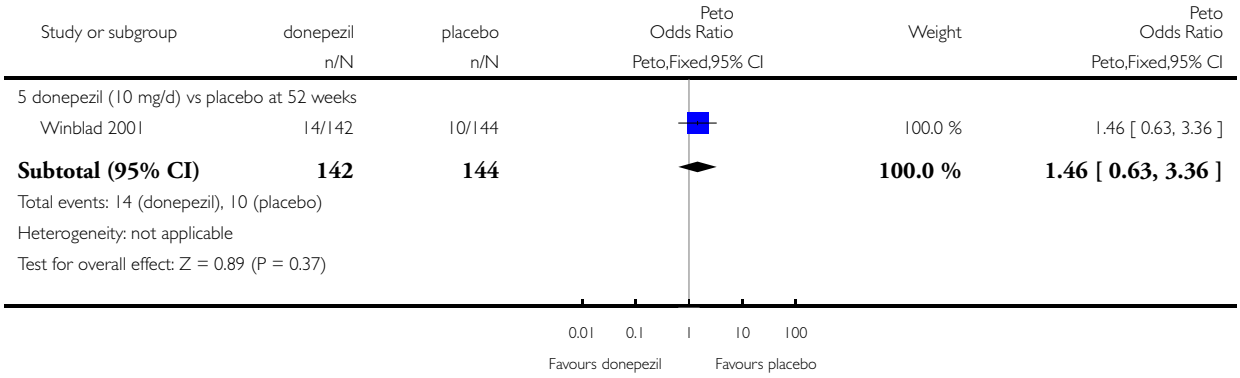
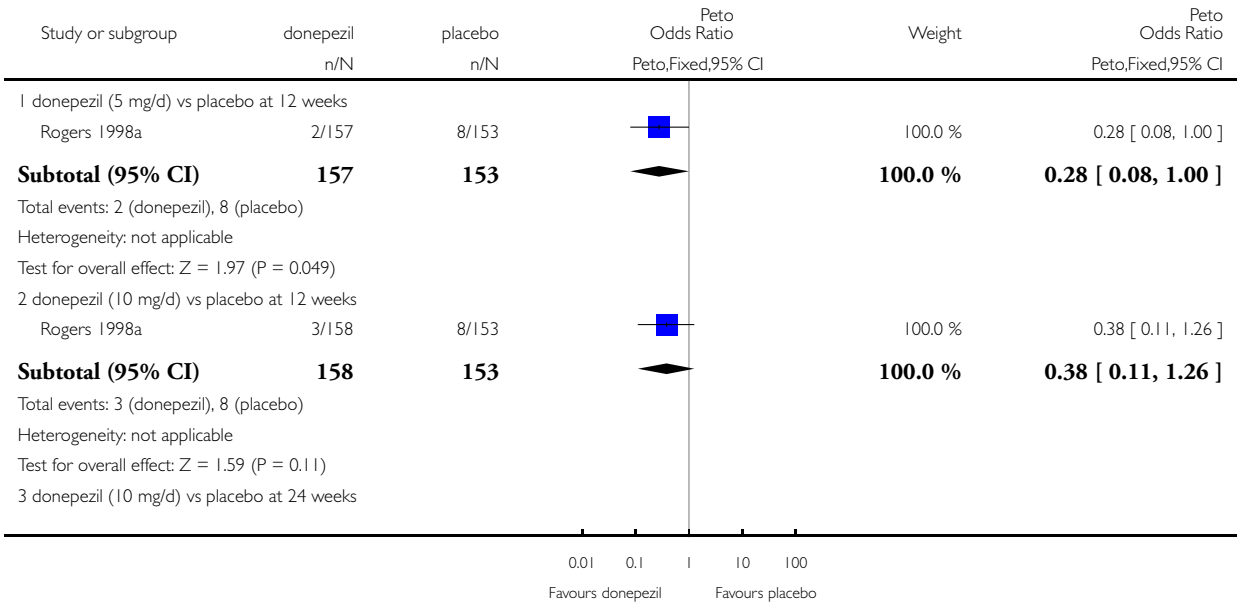


Analysis 2.63. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 63 Total number of participants who suffered from increased cough.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 63 Total number of participants who suffered from increased cough



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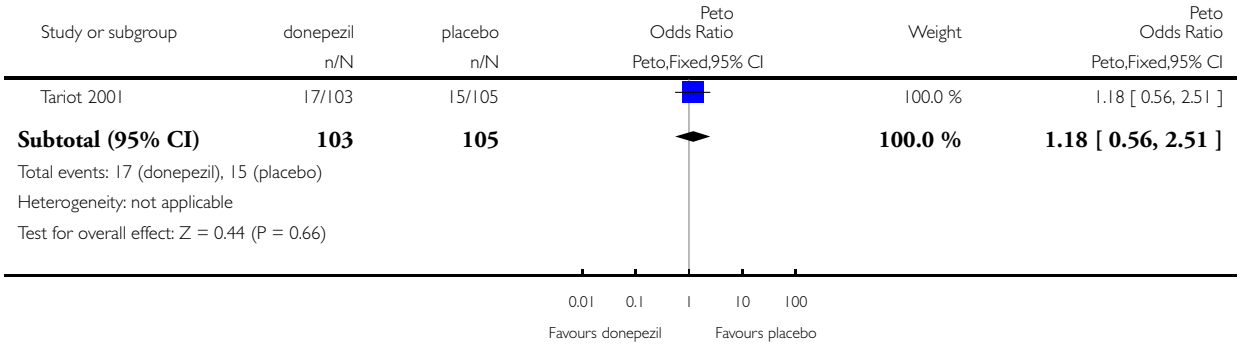
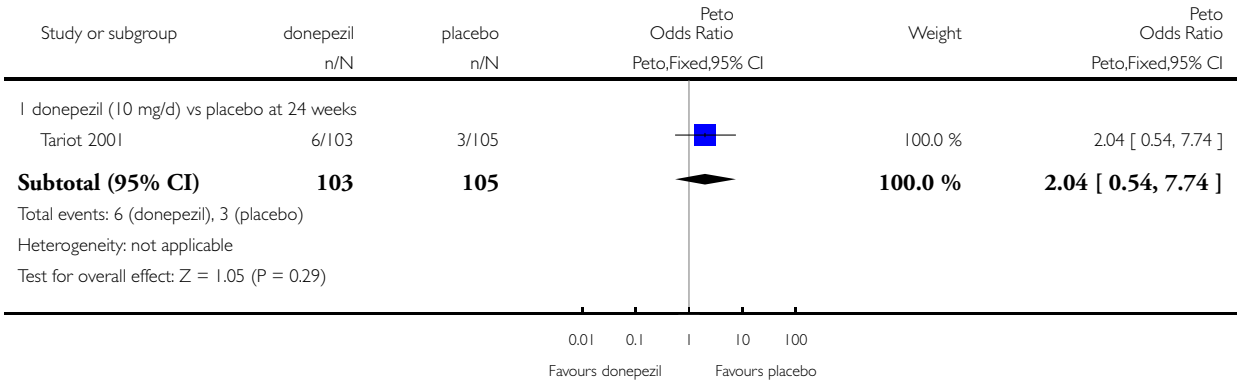


Analysis 2.64. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 64 Total number of participants who suffered from myasthenia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 64 Total number of participants who suffered from myasthenia



Analysis 2.65. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 65 Total number of participants who suffered from muscle cramp.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 65 Total number of participants who suffered from muscle cramp

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks					
Rogers 1998a	9/157	6/153		100.0 %	1.48 [0.53, 4.17]
Subtotal (95% CI)	**157**	**153**		**100.0 %**	**1.48 [0.53, 4.17]**
Total events: 9 (donepezil), 6 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 donepezil (5 mg/d) vs placebo at 24 weeks					
Rogers 1998b	9/154	1/162		100.0 %	5.48 [1.56, 19.27]
Subtotal (95% CI)	**154**	**162**		**100.0 %**	**5.48 [1.56, 19.27]**
Total events: 9 (donepezil), 1 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.65 (P = 0.0081)					
3 donepezil (10 mg/d) vs placebo at 12 weeks					
Rogers 1998a	12/158	6/153		100.0 %	1.96 [0.76, 5.06]
Subtotal (95% CI)	**158**	**153**		**100.0 %**	**1.96 [0.76, 5.06]**
Total events: 12 (donepezil), 6 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
4 donepezil (10 mg/d) vs placebo at 24 weeks					
Rogers 1998b	12/157	1/162		100.0 %	6.00 [1.98, 18.18]
Subtotal (95% CI)	**157**	**162**		**100.0 %**	**6.00 [1.98, 18.18]**
Total events: 12 (donepezil), 1 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.17 (P = 0.0015)					

Analysis 2.66. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 66 Total number of participants who suffered from nausea.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 66 Total number of participants who suffered from nausea

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks					
Homma 1998	6/64	1/59		19.8 %	4.13 [0.90, 18.92]
Rogers 1996	4/40	2/40		16.7 %	2.04 [0.39, 10.65]
Rogers 1998a	11/157	12/153		63.5 %	0.89 [0.38, 2.07]
Subtotal (95% CI)	**261**	**252**		**100.0 %**	**1.38 [0.70, 2.71]**
Total events: 21 (donepezil), 15 (placebo)					
Heterogeneity: Chi^2 = 3.26, df = 2 (P = 0.20); I^2 =39%					
Test for overall effect: Z = 0.93 (P = 0.35)					
2 donepezil (5 mg/d) vs placebo at 24 weeks					
Burns 1999	20/271	19/274		66.3 %	1.07 [0.56, 2.05]
Homma 2000	6/136	1/131		12.5 %	4.15 [0.93, 18.59]
Rogers 1998b	6/154	6/162		21.2 %	1.05 [0.33, 3.34]
Subtotal (95% CI)	**561**	**567**		**100.0 %**	**1.26 [0.74, 2.15]**
Total events: 32 (donepezil), 26 (placebo)					
Heterogeneity: Chi^2 = 2.77, df = 2 (P = 0.25); I^2 =28%					
Test for overall effect: Z = 0.86 (P = 0.39)					
3 donepezil (10 mg/d) vs placebo at 12 weeks					
Rogers 1998a	34/158	12/153		100.0 %	2.95 [1.58, 5.51]
Subtotal (95% CI)	**158**	**153**		**100.0 %**	**2.95 [1.58, 5.51]**
Total events: 34 (donepezil), 12 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.39 (P = 0.00070)					
4 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	13/176	3/167		9.0 %	3.50 [1.29, 9.54]
Burns 1999	66/273	19/274		42.6 %	3.71 [2.34, 5.89]
Feldman 2001	10/120	6/117		8.9 %	1.66 [0.60, 4.57]
Maher-Edwards 2011	2/67	1/62		1.7 %	1.82 [0.19, 17.85]
Rogers 1998b	26/157	6/162		17.1 %	4.14 [1.99, 8.58]
Seltzer 2004	10/96	2/57		6.2 %	2.58 [0.77, 8.71]

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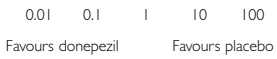
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Tariot 2001	9/103	4/105		7.2 %	2.31 [0.75, 7.08]
Winblad 2006	8/128	5/120		7.3 %	1.52 [0.50, 4.63]
Subtotal (95% CI)	**1120**	**1064**		**100.0 %**	**3.06 [2.26, 4.14]**
Total events: 144 (donepezil), 46 (placebo)					
Heterogeneity: Chi^2 = 4.83, df = 7 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 7.27 (P < 0.00001)					
5 donepezil (10 mg/d) vs placebo at 52 weeks					
Winblad 2001	16/142	13/144		100.0 %	1.28 [0.59, 2.75]
Subtotal (95% CI)	**142**	**144**		**100.0 %**	**1.28 [0.59, 2.75]**
Total events: 16 (donepezil), 13 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					

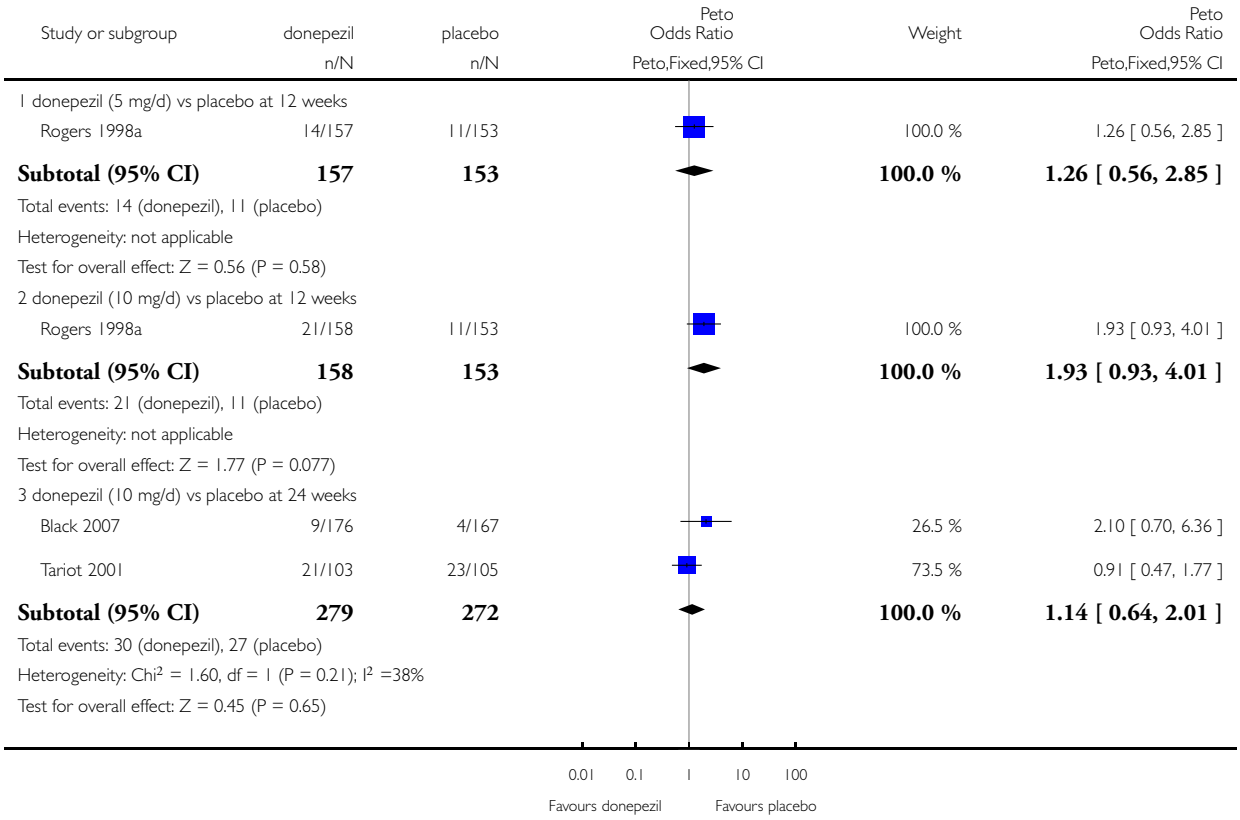


Analysis 2.67. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 67 Total number of participants who suffered from pain.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 67 Total number of participants who suffered from pain

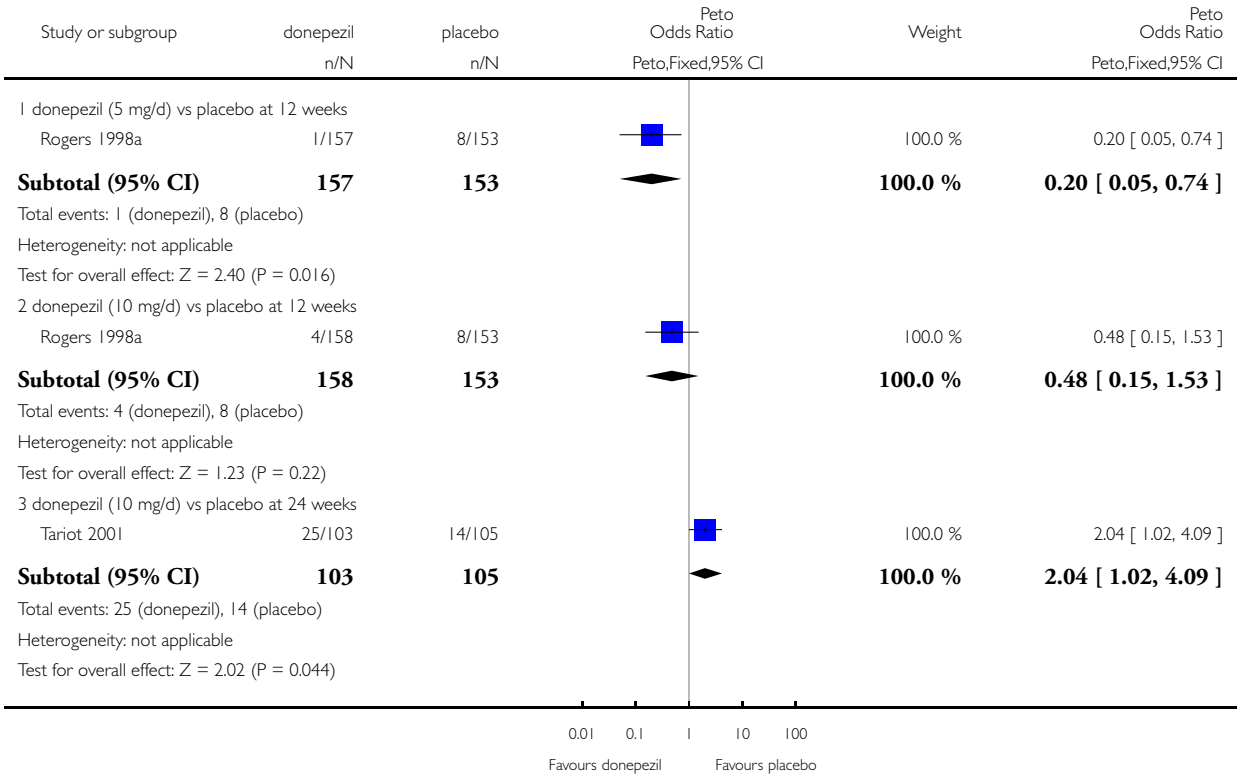


Analysis 2.68. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 68 Total number of participants who suffered from peripheral oedema.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 68 Total number of participants who suffered from peripheral oedema

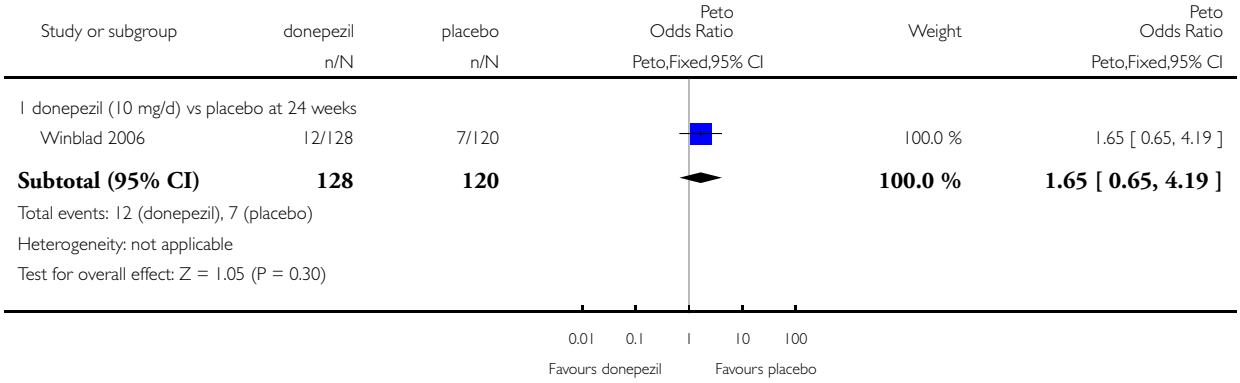


Analysis 2.69. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 69 Total number of participants who suffered from pneumonia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 69 Total number of participants who suffered from pneumonia

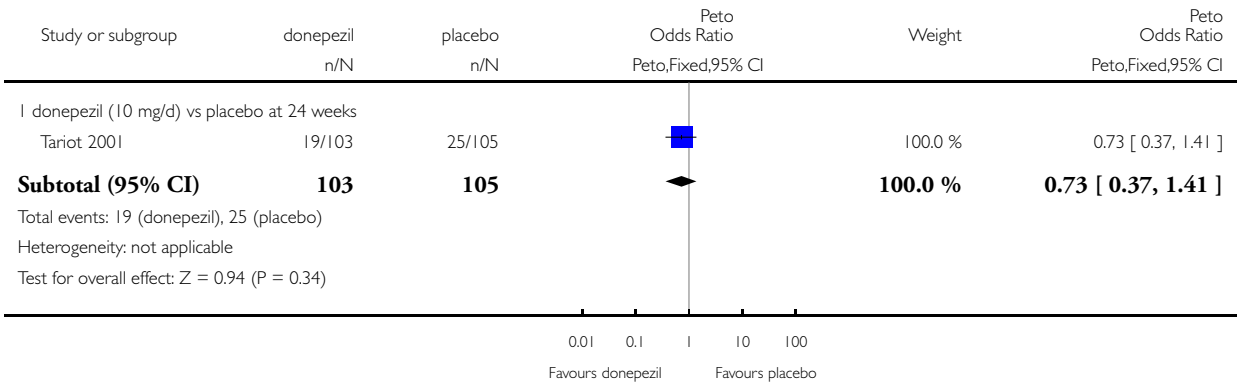


Analysis 2.70. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 70 Total number of participants who suffered from rash.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 70 Total number of participants who suffered from rash

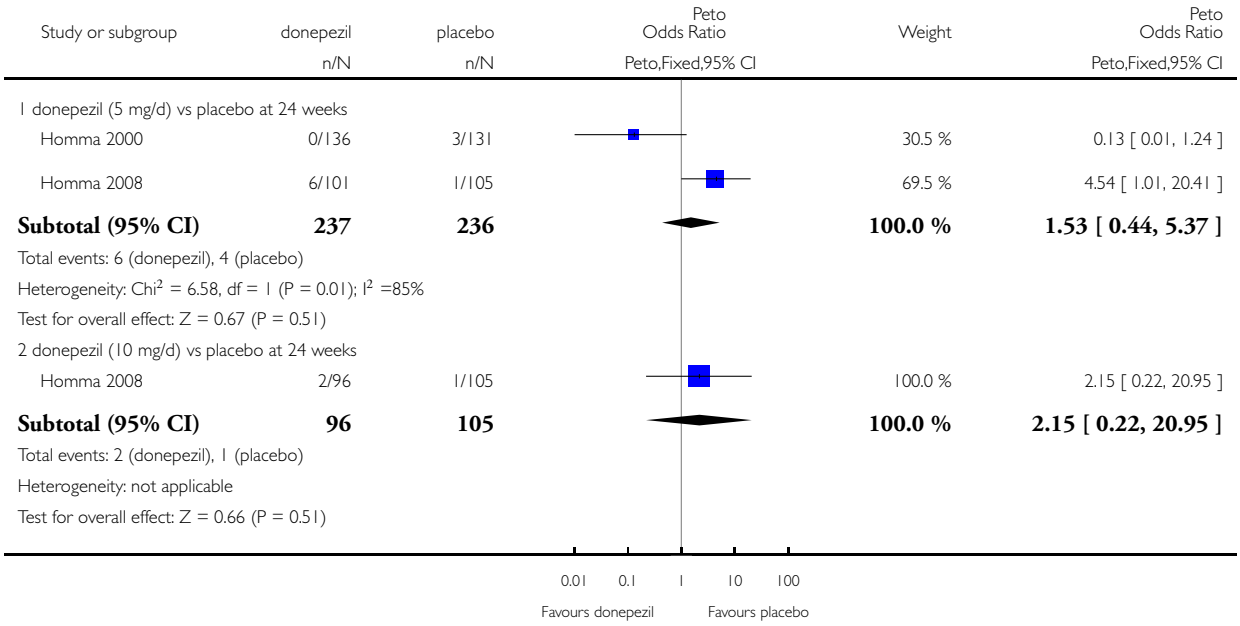


Analysis 2.71. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 71 Total number of participants who suffered from restlessness.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 71 Total number of participants who suffered from restlessness

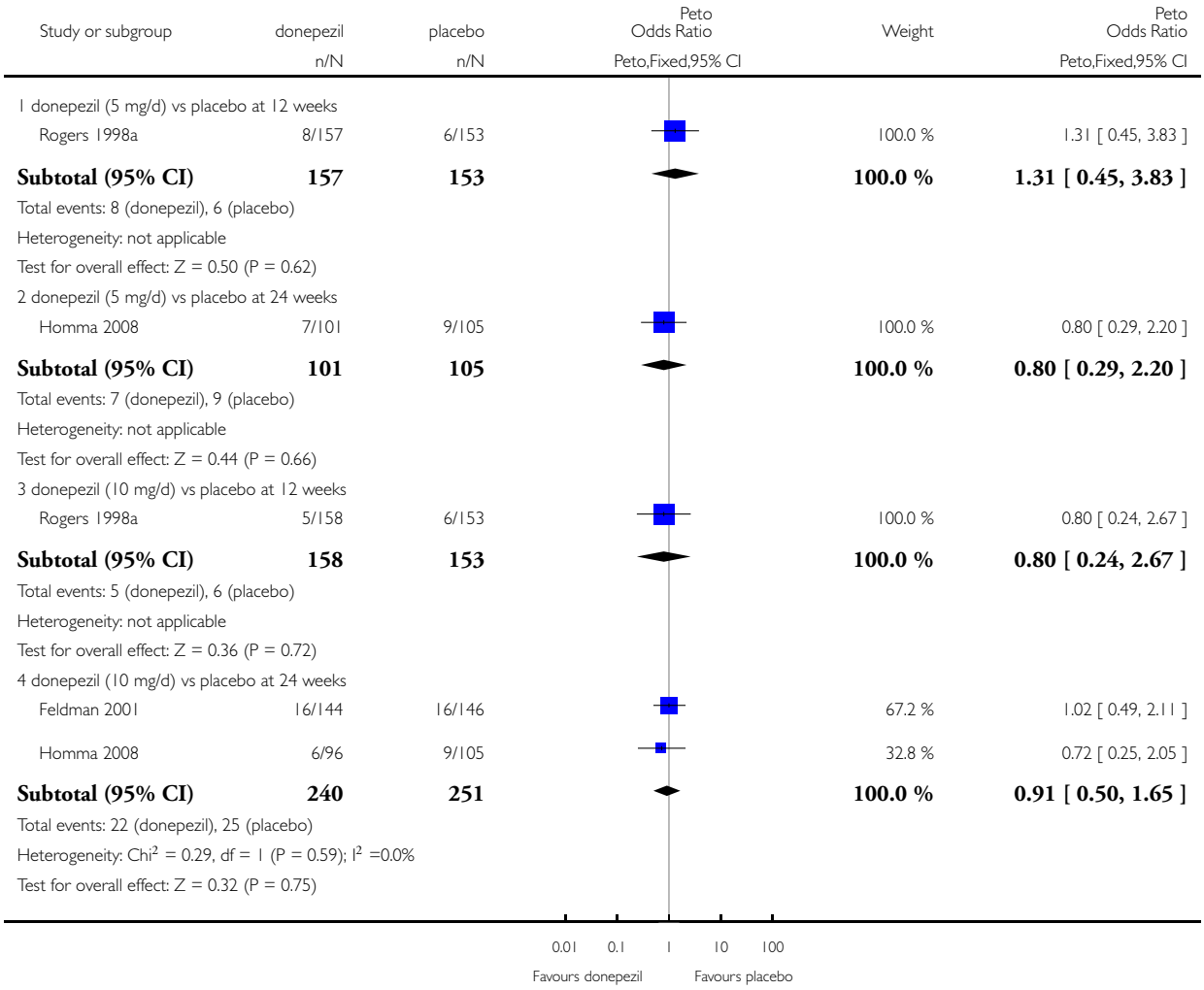


Analysis 2.72. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 72 Total number of participants who suffered from respiratory tract infection.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 72 Total number of participants who suffered from respiratory tract infection

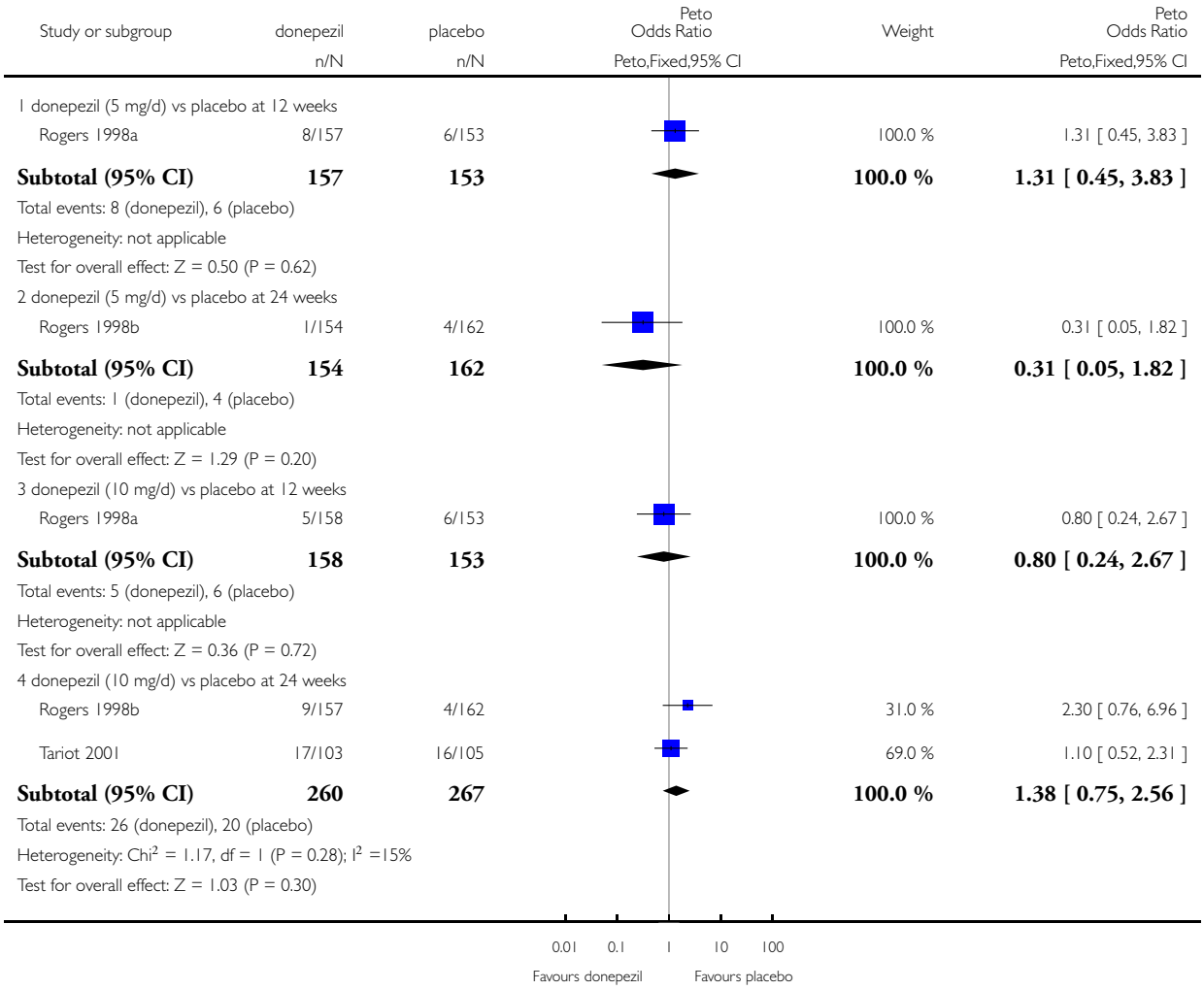


Analysis 2.73. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 73 Total number of participants who suffered from rhinitis.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 73 Total number of participants who suffered from rhinitis

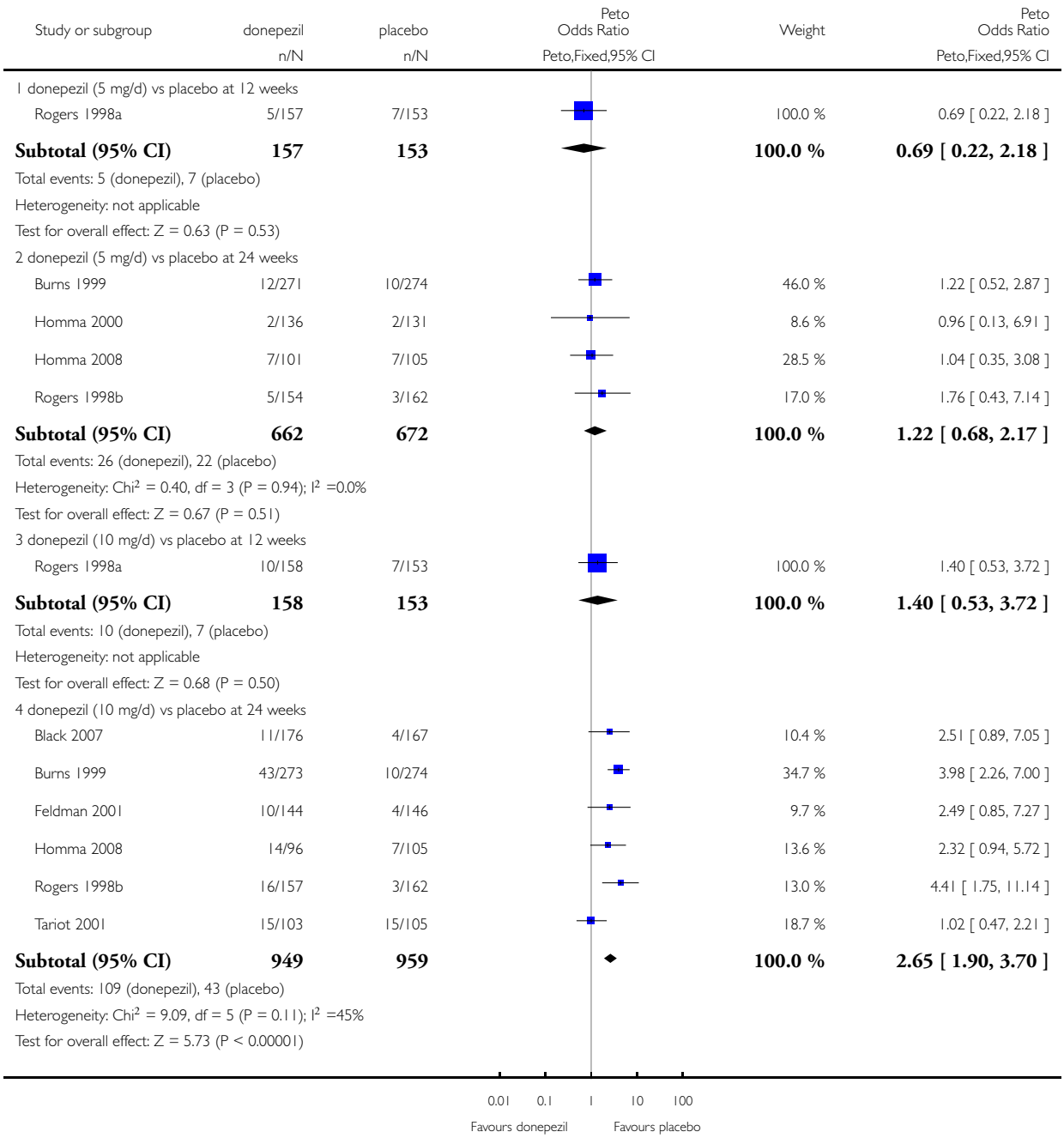


Analysis 2.74. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 74 Total number of participants who suffered from vomiting.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 74 Total number of participants who suffered from vomiting

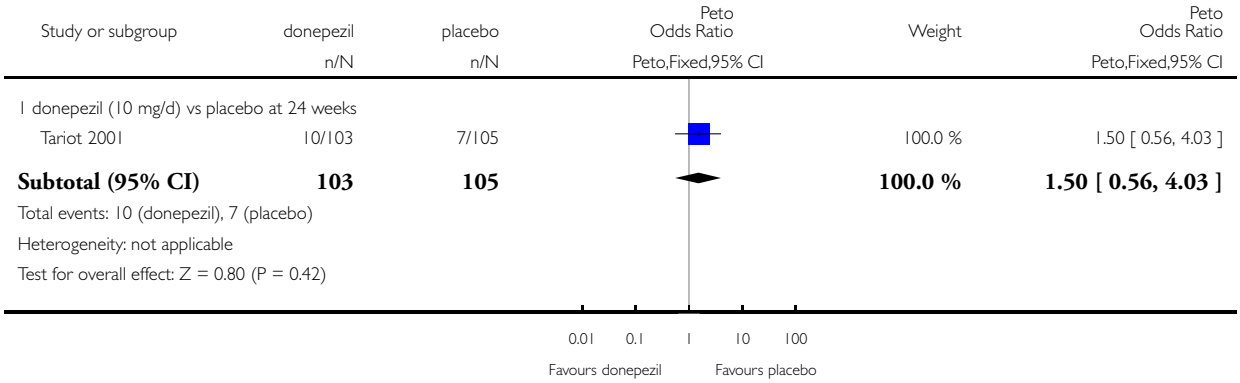


Analysis 2.75. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 75 Total number of participants who suffered from skin ulcer.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 75 Total number of participants who suffered from skin ulcer



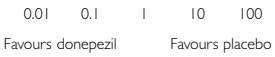
Analysis 2.76. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 76 Total number of participants who suffered from syncope.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 76 Total number of participants who suffered from syncope

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 52 weeks					
Winblad 2001	9/142	4/144		100.0 %	2.27 [0.75, 6.88]
Subtotal (95% CI)	**142**	**144**		**100.0 %**	**2.27 [0.75, 6.88]**
Total events: 9 (donepezil), 4 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.44 (P = 0.15)					



Analysis 2.77. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 77 Total number of participants who suffered from tremor.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 77 Total number of participants who suffered from tremor

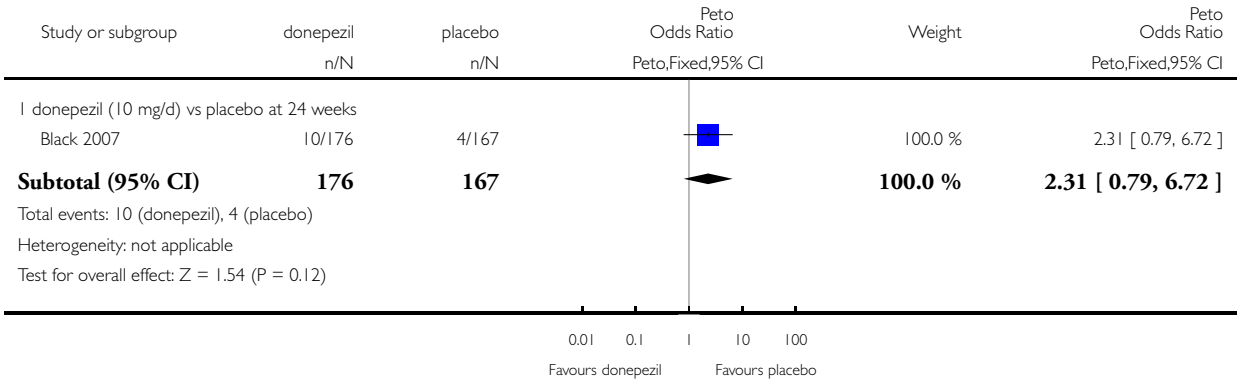
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks					
Tariot 2001	8/103	2/105		100.0 %	3.58 [1.01, 12.71]
Subtotal (95% CI)	**103**	**105**		**100.0 %**	**3.58 [1.01, 12.71]**
Total events: 8 (donepezil), 2 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.97 (P = 0.049)					

Analysis 2.78. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 78 Total number of participants who suffered from urinary incontinence.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 78 Total number of participants who suffered from urinary incontinence

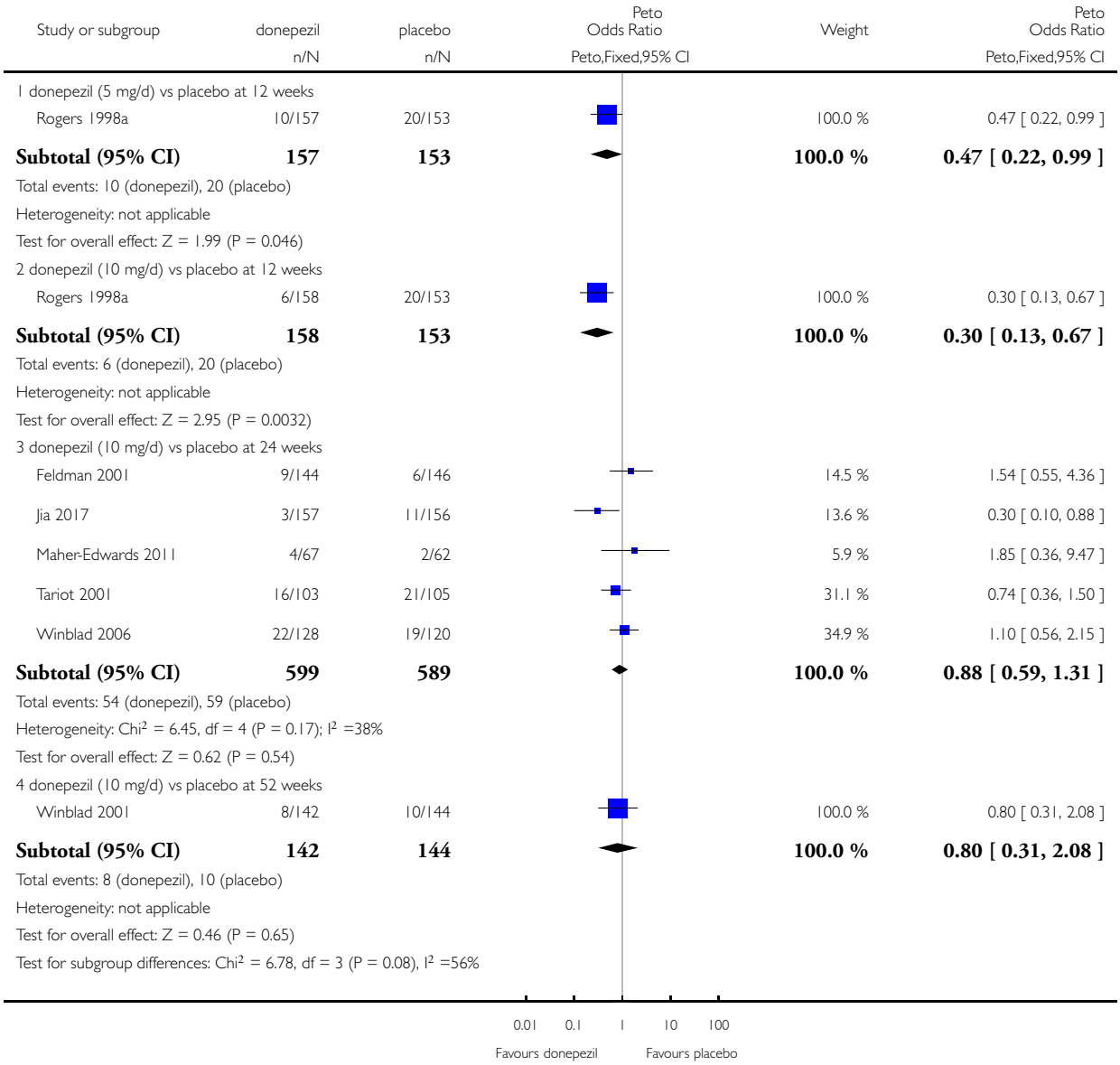


Analysis 2.79. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 79 Total number of participants who suffered from urinary tract infection.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 79 Total number of participants who suffered from urinary tract infection



Analysis 2.80. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 80 Total number of participants who suffered from vertigo.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 80 Total number of participants who suffered from vertigo

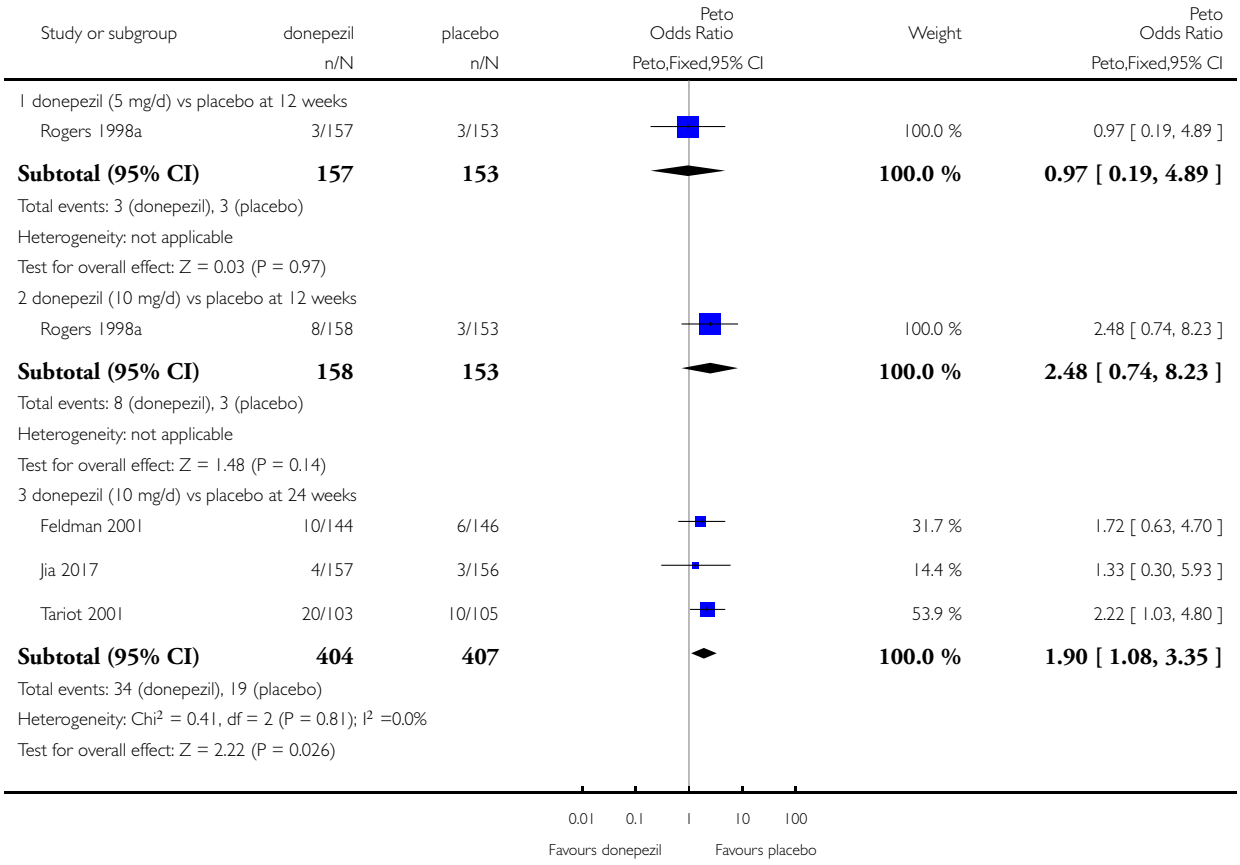
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 52 weeks					
Winblad 2001	11/142	3/144		100.0 %	3.36 [1.15, 9.82]
Subtotal (95% CI)	**142**	**144**		**100.0 %**	**3.36 [1.15, 9.82]**
Total events: 11 (donepezil), 3 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.22 (P = 0.027)					

Analysis 2.81. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 81 Total number of participants who suffered from weight loss.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 81 Total number of participants who suffered from weight loss

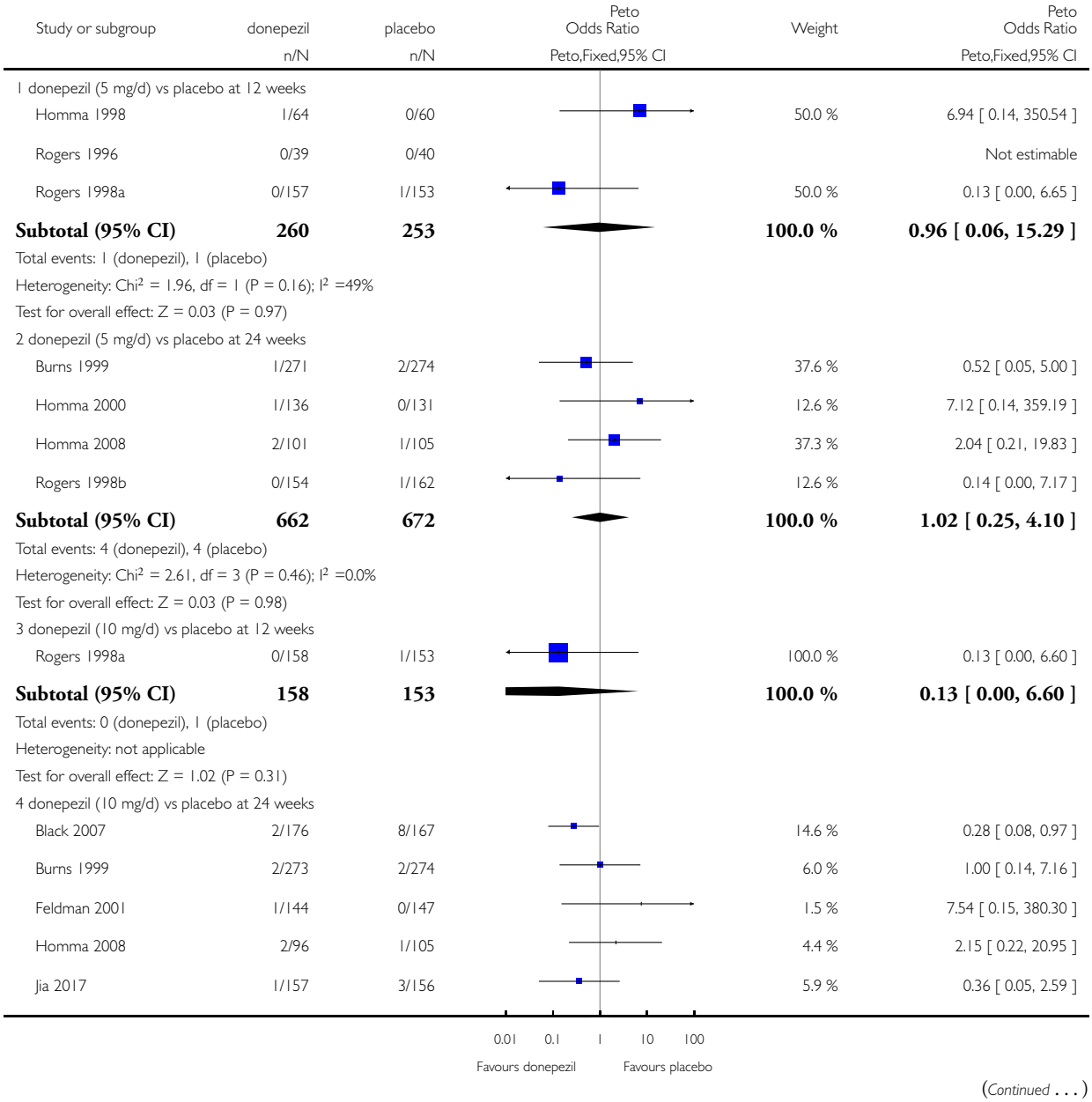


Analysis 2.82. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 82 total number of deaths before end of treatment.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 82 total number of deaths before end of treatment



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Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Krishnan 2003	0/34	0/33			Not estimable
Maher-Edwards 2011	2/67	0/62		3.0 %	6.96 [0.43, 112.77]
Rogers 1998b	1/157	1/162		3.0 %	1.03 [0.06, 16.58]
Seltzer 2004	0/96	0/57			Not estimable
Tariot 2001	3/103	7/105		14.3 %	0.44 [0.12, 1.57]
Tune 2003	0/14	0/14			Not estimable
Winblad 2006	18/128	19/120		47.3 %	0.87 [0.43, 1.75]
Subtotal (95% CI)	**1445**	**1402**		**100.0 %**	**0.74 [0.46, 1.19]**
Total events: 32 (donepezil), 41 (placebo)					
Heterogeneity: Chi^2 = 8.54, df = 8 (P = 0.38); I^2 =6%					
Test for overall effect: Z = 1.26 (P = 0.21)					
5 donepezil (10 mg/d) vs placebo at 52 weeks					
Winblad 2001	4/142	3/144		100.0 %	1.36 [0.30, 6.07]
Subtotal (95% CI)	**142**	**144**		**100.0 %**	**1.36 [0.30, 6.07]**
Total events: 4 (donepezil), 3 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.40 (P = 0.69)					

Analysis 2.83. Comparison 2 Donepezil (5 mg/day or 10 mg/day) versus placebo, Outcome 83 Total number of participants who suffered from at least one serious adverse event.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 2 Donepezil (5 mg/day or 10 mg/day) versus placebo

Outcome: 83 Total number of participants who suffered from at least one serious adverse event

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 12 weeks					
Rogers 1998a	6/157	7/153		100.0 %	0.83 [0.27, 2.51]
Subtotal (95% CI)	**157**	**153**		**100.0 %**	**0.83 [0.27, 2.51]**
Total events: 6 (donepezil), 7 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
2 donepezil (5 mg/d) vs placebo at 24 weeks					
Burns 1999	18/271	25/274		50.6 %	0.71 [0.38, 1.32]
Homma 2008	12/101	15/105		30.0 %	0.81 [0.36, 1.82]
Rogers 1998b	7/154	9/162		19.4 %	0.81 [0.30, 2.21]
Subtotal (95% CI)	**526**	**541**		**100.0 %**	**0.76 [0.49, 1.18]**
Total events: 37 (donepezil), 49 (placebo)					
Heterogeneity: Chi^2 = 0.08, df = 2 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 1.22 (P = 0.22)					
3 donepezil (10 mg/d) vs placebo at 12 weeks					
Rogers 1998a	6/158	7/153		100.0 %	0.82 [0.27, 2.50]
Subtotal (95% CI)	**158**	**153**		**100.0 %**	**0.82 [0.27, 2.50]**
Total events: 6 (donepezil), 7 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					
4 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	20/176	25/167		14.7 %	0.73 [0.39, 1.36]
Burns 1999	29/273	25/274		18.2 %	1.18 [0.67, 2.07]
Feldman 2001	18/144	17/147		11.6 %	1.09 [0.54, 2.21]
Homma 2008	10/96	15/105		8.2 %	0.70 [0.30, 1.62]
Jia 2017	11/157	19/156		10.2 %	0.55 [0.26, 1.17]
Maher-Edwards 2011	4/67	3/62		2.5 %	1.24 [0.27, 5.68]
Rogers 1998b	15/157	9/162		8.3 %	1.77 [0.77, 4.07]
Tariot 2001	10/103	17/105		8.8 %	0.56 [0.25, 1.27]

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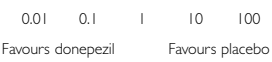
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Winblad 2006	31/128	31/120		17.5 %	0.92 [0.52, 1.63]
Subtotal (95% CI)	**1301**	**1298**		**100.0 %**	**0.90 [0.71, 1.14]**
Total events: 148 (donepezil), 161 (placebo)					
Heterogeneity: Chi^2 = 7.62, df = 8 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 0.88 (P = 0.38)					
5 donepezil (10 mg/d) vs placebo at 52 weeks					
Winblad 2001	35/142	20/144		100.0 %	1.99 [1.11, 3.59]
Subtotal (95% CI)	**142**	**144**		**100.0 %**	**1.99 [1.11, 3.59]**
Total events: 35 (donepezil), 20 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.30 (P = 0.021)					



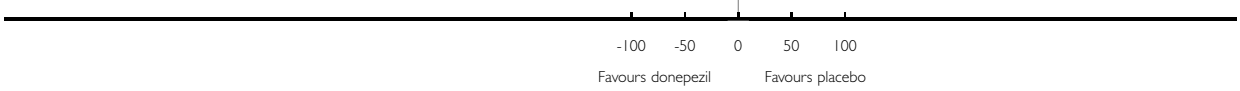
Analysis 3.1. Comparison 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation), Outcome 1 Patient and carer health resource utilisation over 24 weeks (Australia, Canada, France).

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation)

Outcome: 1 Patient and carer health resource utilisation over 24 weeks (Australia, Canada, France)

Study or subgroup	Donepezil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In-home nursing visits							
Feldman 2001	143	2.2 (14.2)	146	1.7 (12.7)		100.0 %	0.50 [-2.61, 3.61]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**0.50 [-2.61, 3.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.32 (P = 0.75)							
2 Other healthcare professional visits							
Feldman 2001	143	0.9 (2.7)	146	2.1 (10.6)		100.0 %	-1.20 [-2.98, 0.58]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**-1.20 [-2.98, 0.58]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.32 (P = 0.19)							
3 Day hospital visits							
Feldman 2001	143	0.5 (3.7)	146	0.5 (2.1)		100.0 %	0.0 [-0.70, 0.70]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**0.0 [-0.70, 0.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
4 AD-related physician visits							
Feldman 2001	143	2.2 (2.2)	146	2.3 (3)		100.0 %	-0.10 [-0.71, 0.51]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**-0.10 [-0.71, 0.51]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.32 (P = 0.75)							
5 AD-related medication							
Feldman 2001	143	0.1 (1.8)	146	0.2 (1.9)		100.0 %	-0.10 [-0.53, 0.33]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**-0.10 [-0.53, 0.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.46 (P = 0.65)							
6 Residential care days							
Feldman 2001	143	11.9 (37.3)	146	18.8 (50.5)		100.0 %	-6.90 [-17.12, 3.32]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**-6.90 [-17.12, 3.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.32 (P = 0.19)							
7 Respite care days							
Feldman 2001	143	1.5 (6.8)	146	0.6 (3.6)		100.0 %	0.90 [-0.36, 2.16]



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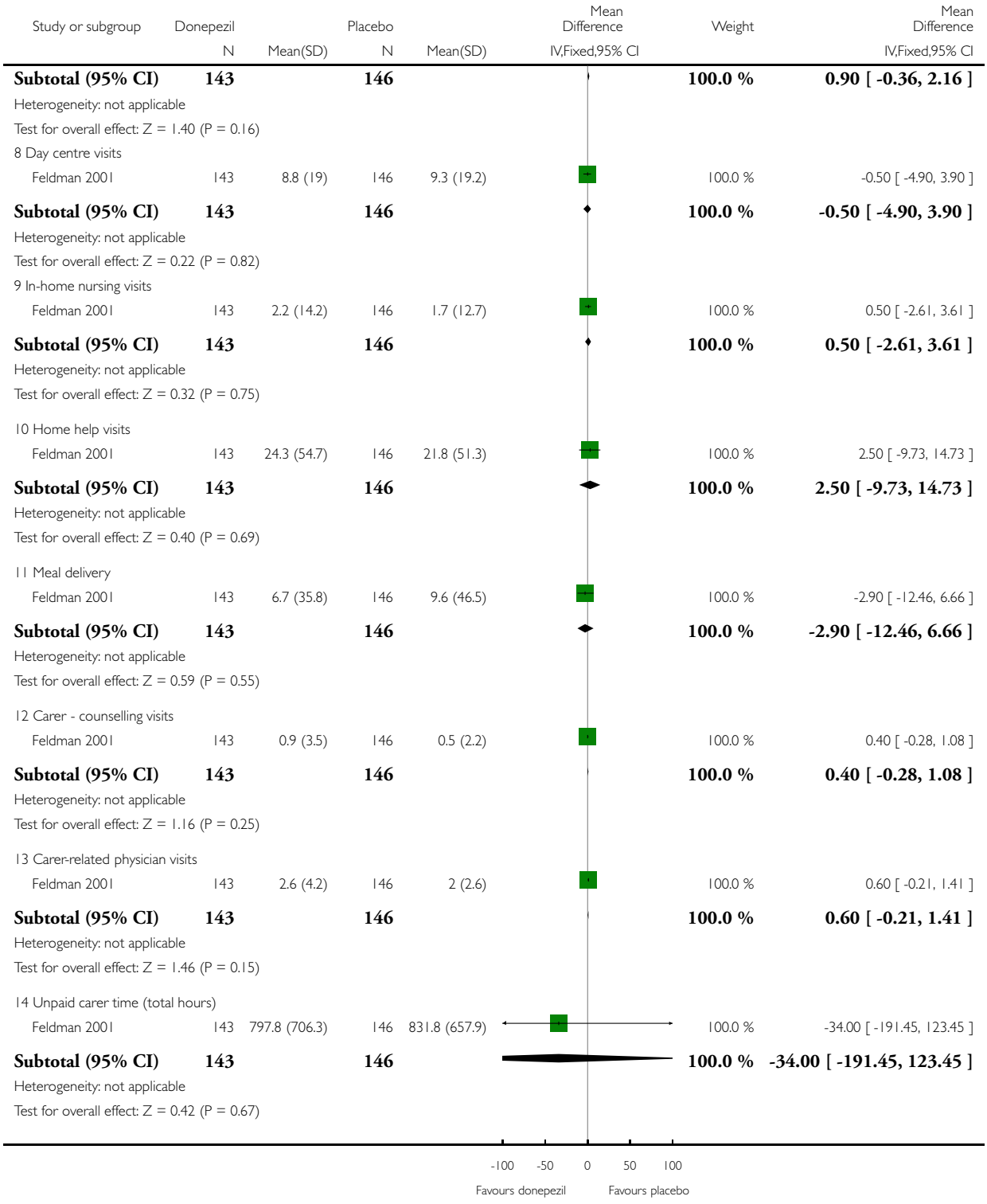

Analysis 3.2. Comparison 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation), Outcome 2 Health resource cost/participant (CAD) over 24 weeks in 1998 (Australia, Canada, France).

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation)

Outcome: 2 Health resource cost/participant (CAD) over 24 weeks in 1998 (Australia, Canada, France)

Study or subgroup	Donepezil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In-home nursing care							
Feldman 2001	143	100 (642)	146	78 (574)		100.0 %	22.00 [-118.50, 162.50]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**22.00 [-118.50, 162.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							
2 Other healthcare professional services							
Feldman 2001	143	44 (136)	146	147 (853)		100.0 %	-103.00 [-243.15, 37.15]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**-103.00 [-243.15, 37.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.44 (P = 0.15)							
3 Day hospital use							
Feldman 2001	143	51 (389)	146	52 (228)		100.0 %	-1.00 [-74.71, 72.71]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**-1.00 [-74.71, 72.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.03 (P = 0.98)							
4 AD-related physician services							
Feldman 2001	143	60 (61)	146	75 (156)		100.0 %	-15.00 [-42.21, 12.21]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**-15.00 [-42.21, 12.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.08 (P = 0.28)							
5 AD-related medication							
Feldman 2001	143	63 (155)	146	38 (105)		100.0 %	25.00 [-5.59, 55.59]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**25.00 [-5.59, 55.59]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.60 (P = 0.11)							
6 Acute-care hospital stays							
Feldman 2001	143	100 (642)	146	78 (574)		100.0 %	22.00 [-118.50, 162.50]

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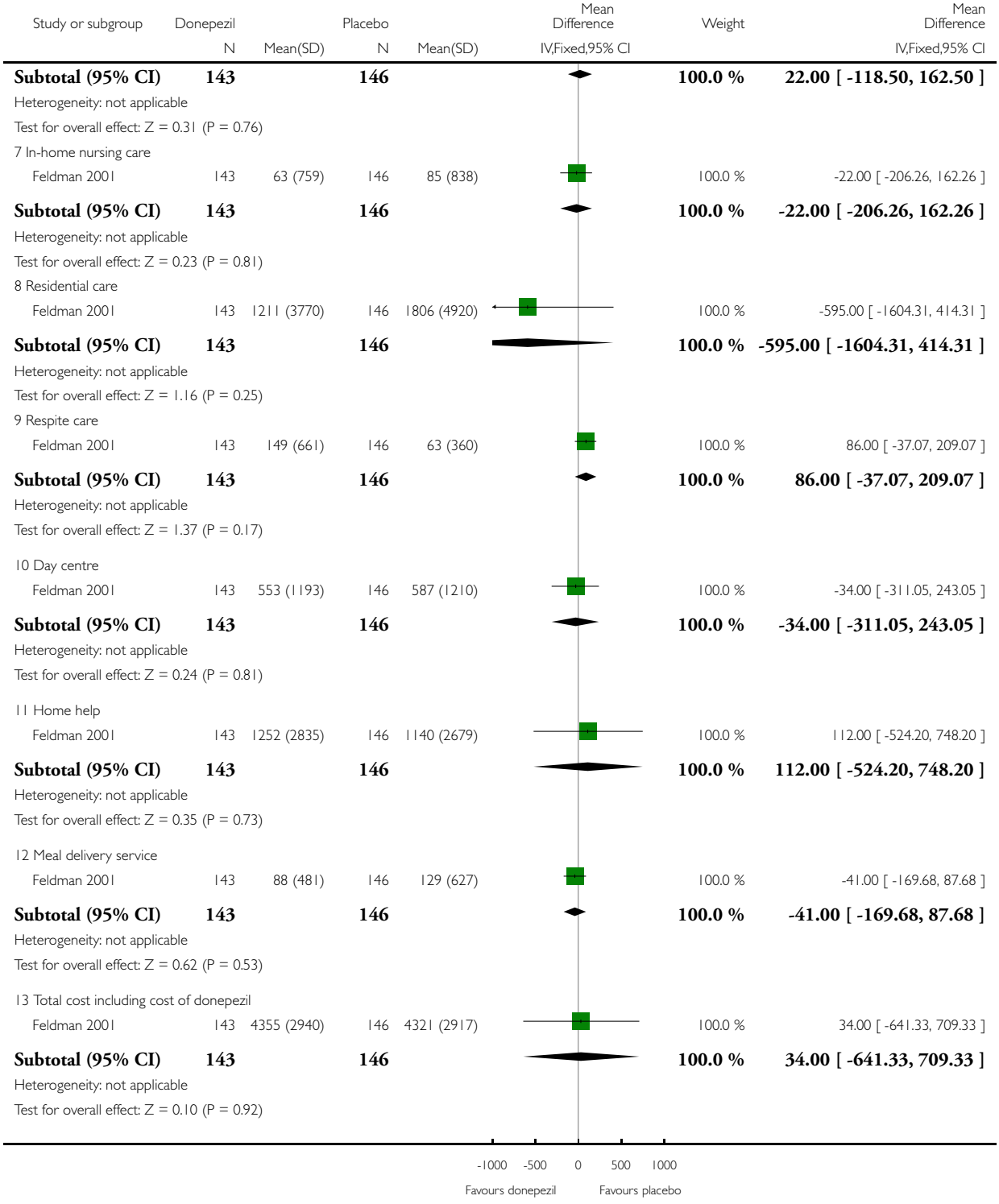
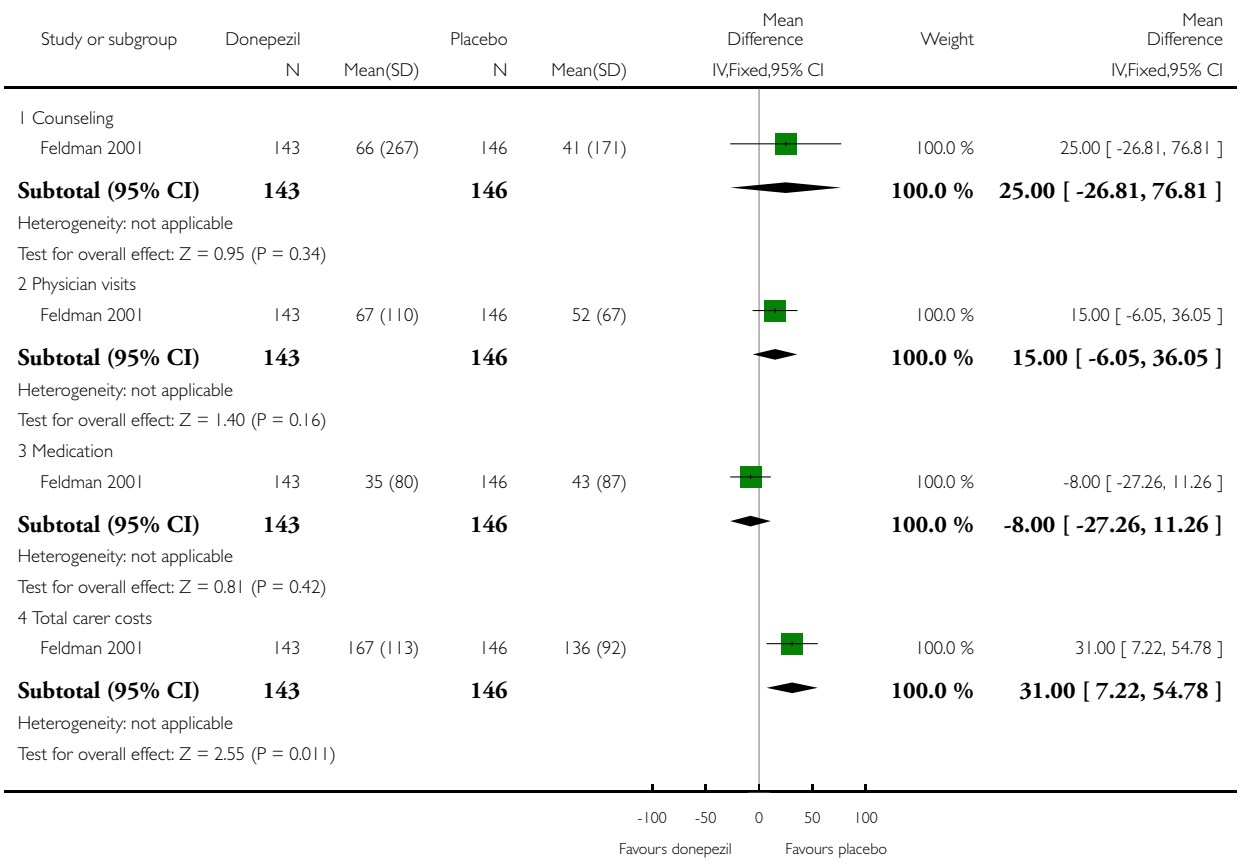


Analysis 3.3. Comparison 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation), Outcome 3 Health resource cost/carer (CAD) over 24 weeks in 1998 (Australia, Canada, France).

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation)

Outcome: 3 Health resource cost/carer (CAD) over 24 weeks in 1998 (Australia, Canada, France)



Analysis 3.4. Comparison 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation), Outcome 4 Unpaid carer time cost (CAD) in 1998 (Australia, Canada, France).

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation)

Outcome: 4 Unpaid carer time cost (CAD) in 1998 (Australia, Canada, France)

Study or subgroup	Donepezil		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Feldman 2001	143	5382 (3633)	146	5779 (3901)			-397.00 [-1265.89, 471.89]

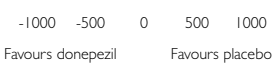
Analysis 3.5. Comparison 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation), Outcome 5 Total cost to society (CAD) in 1998 (Australia, Canada, France).

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation)

Outcome: 5 Total cost to society (CAD) in 1998 (Australia, Canada, France)

Study or subgroup	Donepezil		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Feldman 2001	143	9904 (6686)	146	10236 (6910)			-332.00 [-1899.54, 1235.54]

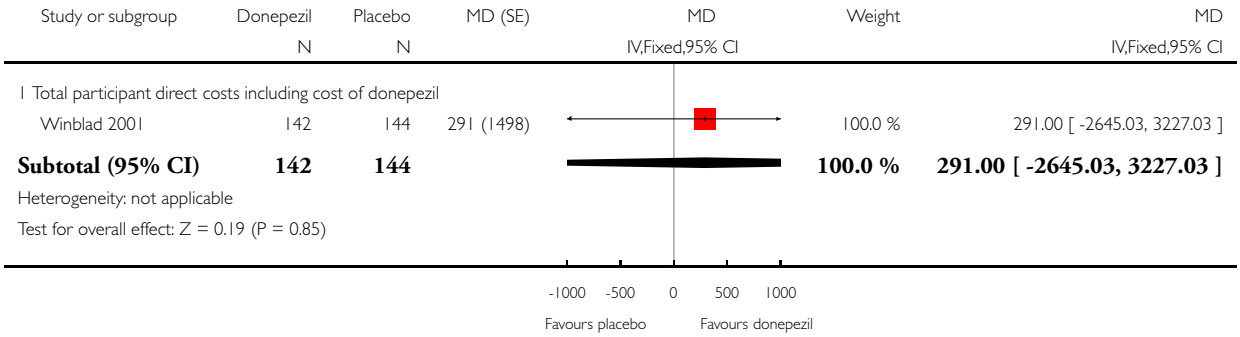


Analysis 3.6. Comparison 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation), Outcome 6 Health resource cost/participant (USD) over one year in 1999 (northern Europe).

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation)

Outcome: 6 Health resource cost/participant (USD) over one year in 1999 (northern Europe)

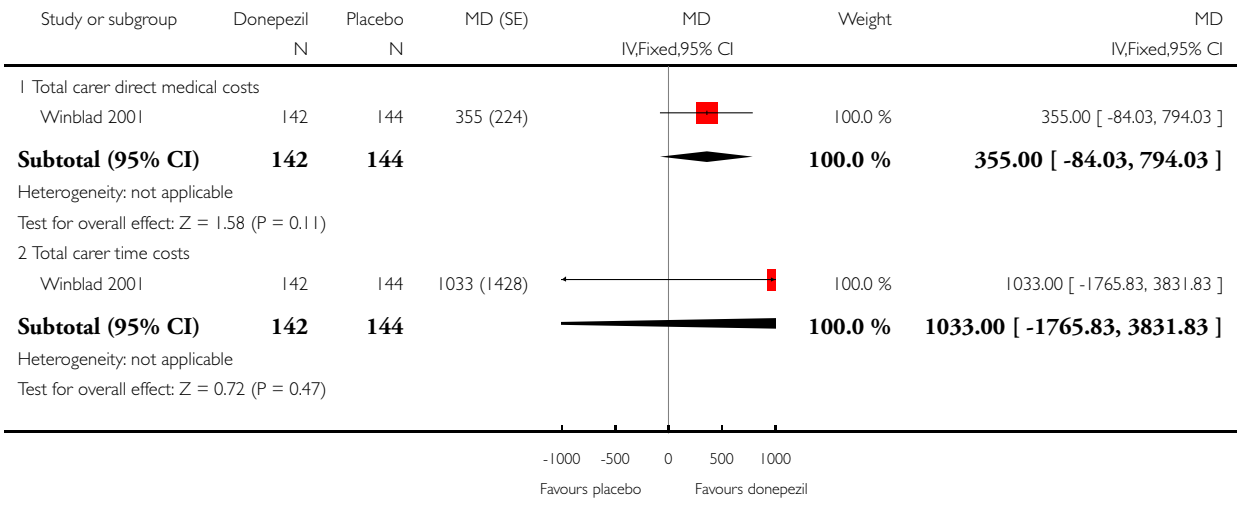


Analysis 3.7. Comparison 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation), Outcome 7 Health resource cost/carer (USD) over one year in 1999 (northern Europe).

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation)

Outcome: 7 Health resource cost/carer (USD) over one year in 1999 (northern Europe)

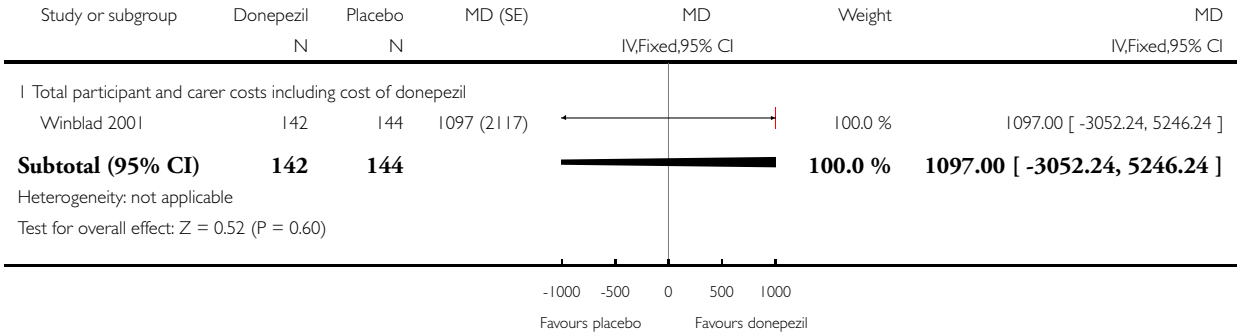


Analysis 3.8. Comparison 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation), Outcome 8 Health resource cost/participant + carer (USD) over one year in 1999 (northern Europe).

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 3 Donepezil (10 mg/day) versus placebo (patient and carer health resource utilisation)

Outcome: 8 Health resource cost/participant + carer (USD) over one year in 1999 (northern Europe)



Analysis 4.1. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 1 SIB (change from baseline) at 24 weeks ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 1 SIB (change from baseline) at 24 weeks ITT-LOCF

Study or subgroup	donepezil (23 mg/day) N	Mean(SD)	donepezil (10 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Farlow 2010	907	2.6 (17.3)	462	0.4 (14.5)		47.8 %	2.20 [0.46, 3.94]
Homma 2016	177	-2.7 (8)	158	-2.7 (7.5)		52.2 %	0.0 [-1.66, 1.66]
Total (95% CI)	**1084**		**620**			**100.0 %**	**1.05 [-0.15, 2.25]**

Heterogeneity: Chi^2 = 3.22, df = 1 (P = 0.07); I^2 =69%

Test for overall effect: Z = 1.72 (P = 0.086)

Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 2 MMSE (change from baseline at 24 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 2 MMSE (change from baseline at 24 weeks) ITT-LOCF

Study or subgroup	donepezil (23 mg/day) N	Mean(SD)	donepezil (10 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Farlow 2010	908	0.4 (5.4)	462	0.2 (4.3)		100.0 %	0.20 [-0.33, 0.73]
Total (95% CI)	**908**		**462**			**100.0 %**	**0.20 [-0.33, 0.73]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 3 ADCS-ADL-sev (change from baseline) at 24 weeks ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 3 ADCS-ADL-sev (change from baseline) at 24 weeks ITT-LOCF

Study or subgroup	donepezil (23 mg/day) N	Mean(SD)	donepezil (10 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Farlow 2010	908	-1.2 (12.1)	461	-1.2 (9.7)		100.0 %	0.0 [-1.18, 1.18]
Total (95% CI)	**908**		**461**			**100.0 %**	**0.0 [-1.18, 1.18]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable

Analysis 4.4. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 4 CIBIC-plus (numbers improved) by end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 4 CIBIC-plus (numbers improved) by end of treatment at 24 weeks

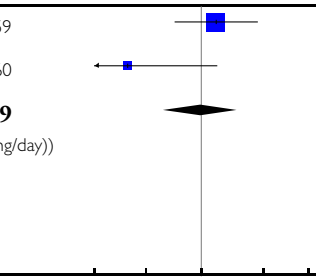
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	210/907	99/459		77.6 %	1.10 [0.84, 1.44]
Homma 2016	24/178	32/160		22.4 %	0.62 [0.35, 1.11]
Total (95% CI)	**1085**	**619**		**100.0 %**	**0.99 [0.78, 1.26]**

Total events: 234 (donepezil (23 mg/day)), 131 (donepezil (10 mg/day))

Heterogeneity: $Chi^2 = 2.99$, df = 1 (P = 0.08); $I^2 = 67\%$

Test for overall effect: Z = 0.08 (P = 0.93)

Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 5 total number of patients who withdrew before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 5 total number of patients who withdrew before end of treatment at 24 weeks

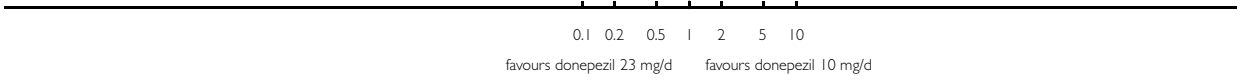
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	296/981	87/486		81.1 %	1.98 [1.51, 2.59]
Homma 2016	52/185	25/166		18.9 %	2.21 [1.29, 3.76]
Total (95% CI)	**1166**	**652**		**100.0 %**	**2.02 [1.59, 2.57]**

Total events: 348 (donepezil (23 mg/day)), 112 (donepezil (10 mg/day))

Heterogeneity: $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 5.75 (P < 0.00001)

Test for subgroup differences: Not applicable



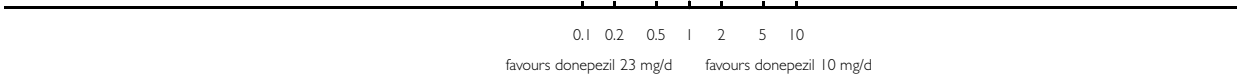
Analysis 4.6. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 6 total number of patients who withdrew due to an adverse event before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 6 total number of patients who withdrew due to an adverse event before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	182/981	39/486		76.6 %	2.61 [1.81, 3.76]
Homma 2016	33/185	15/166		23.4 %	2.19 [1.14, 4.19]
Total (95% CI)	**1166**	**652**		**100.0 %**	**2.51 [1.83, 3.45]**
Total events: 215 (donepezil (23 mg/day)), 54 (donepezil (10 mg/day))					
Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 5.68 (P < 0.00001)					
Test for subgroup differences: Not applicable					



Analysis 4.7. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 7 total number of patients who suffered an adverse event before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 7 total number of patients who suffered an adverse event before end of treatment at 24 weeks

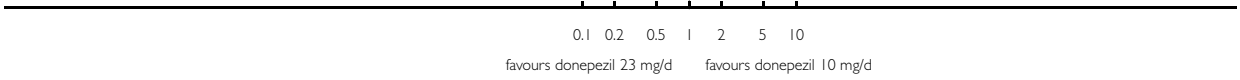
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	710/963	300/471		78.8 %	1.60 [1.26, 2.03]
Homma 2016	134/185	98/166		21.2 %	1.82 [1.17, 2.85]
Total (95% CI)	**1148**	**637**		**100.0 %**	**1.65 [1.34, 2.03]**

Total events: 844 (donepezil (23 mg/day)), 398 (donepezil (10 mg/day))

Heterogeneity: $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 4.68 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 4.8. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 8 total number of patients who suffered a serious adverse event before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 8 total number of patients who suffered a serious adverse event before end of treatment at 24 weeks

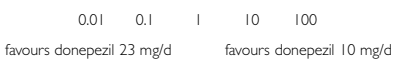
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	80/963	45/471		81.1 %	0.86 [0.58, 1.26]
Homma 2016	23/185	14/166		18.9 %	1.54 [0.77, 3.10]
Total (95% CI)	**1148**	**637**		**100.0 %**	**0.99 [0.71, 1.38]**

Total events: 103 (donepezil (23 mg/day)), 59 (donepezil (10 mg/day))

Heterogeneity: Chi^2 = 2.07, df = 1 (P = 0.15); I^2 =52%

Test for overall effect: Z = 0.08 (P = 0.94)

Test for subgroup differences: Not applicable



Analysis 4.9. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 9 total number of patients who suffered an adverse event of asthenia before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 9 total number of patients who suffered an adverse event of asthenia before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	20/963	3/471		100.0 %	3.31 [0.98, 11.19]
Total (95% CI)	**963**	**471**		**100.0 %**	**3.31 [0.98, 11.19]**

Total events: 20 (donepezil (23 mg/day)), 3 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 1.92 (P = 0.054)

Test for subgroup differences: Not applicable

Analysis 4.10. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 10 total number of patients who suffered an adverse event of contusion before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 10 total number of patients who suffered an adverse event of contusion before end of treatment at 24 weeks

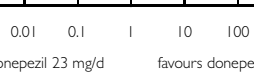
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	20/963	1/471		25.2 %	9.97 [1.33, 74.50]
Homma 2016	14/185	4/166		74.8 %	3.32 [1.07, 10.28]
Total (95% CI)	**1148**	**637**		**100.0 %**	**4.99 [1.88, 13.26]**

Total events: 34 (donepezil (23 mg/day)), 5 (donepezil (10 mg/day))

Heterogeneity: $Chi^2 = 0.96$, df = 1 (P = 0.33); $I^2 = 0.0\%$

Test for overall effect: Z = 3.23 (P = 0.0012)

Test for subgroup differences: Not applicable



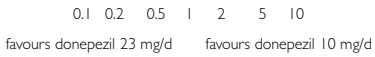
Analysis 4.11. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 11 total number of patients who suffered an adverse event of anorexia before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 11 total number of patients who suffered an adverse event of anorexia before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	51/963	8/471		100.0 %	3.24 [1.52, 6.88]
Total (95% CI)	**963**	**471**		**100.0 %**	**3.24 [1.52, 6.88]**
Total events: 51 (donepezil (23 mg/day)), 8 (donepezil (10 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.05 (P = 0.0023)					
Test for subgroup differences: Not applicable					



Analysis 4.12. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 12 total number of patients who suffered an adverse event of diarrhoea before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 12 total number of patients who suffered an adverse event of diarrhoea before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	80/963	25/471		86.3 %	1.62 [1.02, 2.57]
Homma 2016	14/185	5/166		13.7 %	2.64 [0.93, 7.49]
Total (95% CI)	**1148**	**637**		**100.0 %**	**1.76 [1.15, 2.68]**
Total events: 94 (donepezil (23 mg/day)), 30 (donepezil (10 mg/day))					
Heterogeneity: Chi^2 = 0.71, df = 1 (P = 0.40); I^2 =0.0%					
Test for overall effect: Z = 2.60 (P = 0.0092)					
Test for subgroup differences: Not applicable					

Analysis 4.13. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 13 total number of patients who suffered an adverse event of dizziness before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 13 total number of patients who suffered an adverse event of dizziness before end of treatment at 24 weeks

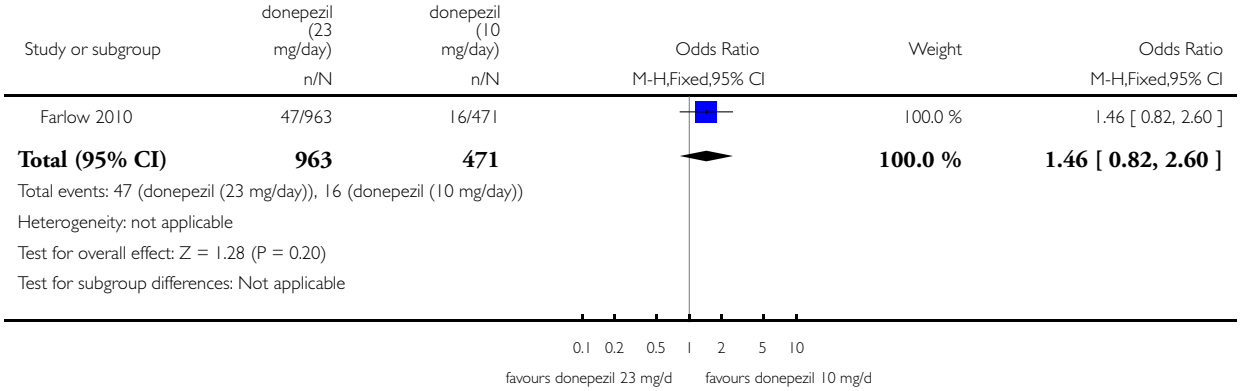
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	47/963	16/471		100.0 %	1.46 [0.82, 2.60]
Total (95% CI)	**963**	**471**		**100.0 %**	**1.46 [0.82, 2.60]**

Total events: 47 (donepezil (23 mg/day)), 16 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable



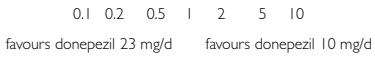
Analysis 4.14. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 14 total number of patients who suffered an adverse event of fatigue before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 14 total number of patients who suffered an adverse event of fatigue before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	23/963	4/471		100.0 %	2.86 [0.98, 8.31]
Total (95% CI)	**963**	**471**		**100.0 %**	**2.86 [0.98, 8.31]**
Total events: 23 (donepezil (23 mg/day)), 4 (donepezil (10 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.054)					
Test for subgroup differences: Not applicable					



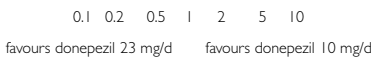
Analysis 4.15. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 15 total number of patients who suffered an adverse event of headache before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 15 total number of patients who suffered an adverse event of headache before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	41/963	15/471		100.0 %	1.35 [0.74, 2.47]
Total (95% CI)	**963**	**471**		**100.0 %**	**1.35 [0.74, 2.47]**
Total events: 41 (donepezil (23 mg/day)), 15 (donepezil (10 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Not applicable					



Analysis 4.16. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 16 total number of patients who suffered an adverse event of insomnia before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 16 total number of patients who suffered an adverse event of insomnia before end of treatment at 24 weeks

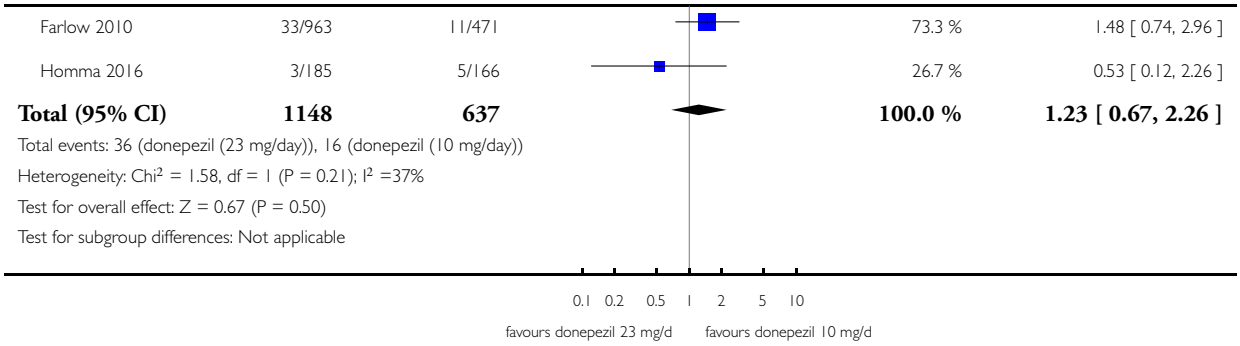
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	33/963	11/471		73.3 %	1.48 [0.74, 2.96]
Homma 2016	3/185	5/166		26.7 %	0.53 [0.12, 2.26]
Total (95% CI)	**1148**	**637**		**100.0 %**	**1.23 [0.67, 2.26]**

Total events: 36 (donepezil (23 mg/day)), 16 (donepezil (10 mg/day))

Heterogeneity: $Chi^2 = 1.58$, df = 1 (P = 0.21); $I^2 = 37\%$

Test for overall effect: Z = 0.67 (P = 0.50)

Test for subgroup differences: Not applicable



Analysis 4.17. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 17 total number of patients who suffered an adverse event of nausea before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 17 total number of patients who suffered an adverse event of nausea before end of treatment at 24 weeks

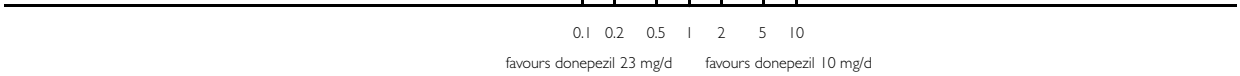
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	114/963	16/471		79.1 %	3.82 [2.24, 6.52]
Homma 2016	9/185	5/166		20.9 %	1.65 [0.54, 5.02]
Total (95% CI)	**1148**	**637**		**100.0 %**	**3.36 [2.09, 5.42]**

Total events: 123 (donepezil (23 mg/day)), 21 (donepezil (10 mg/day))

Heterogeneity: Chi^2 = 1.80, df = 1 (P = 0.18); I^2 =44%

Test for overall effect: Z = 4.98 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 4.18. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 18 total number of patients who suffered an adverse event of vomiting before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 18 total number of patients who suffered an adverse event of vomiting before end of treatment at 24 weeks

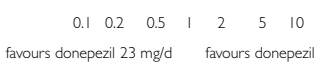
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	89/963	12/471		79.2 %	3.90 [2.11, 7.19]
Homma 2016	16/185	4/166		20.8 %	3.83 [1.26, 11.71]
Total (95% CI)	**1148**	**637**		**100.0 %**	**3.88 [2.27, 6.65]**

Total events: 105 (donepezil (23 mg/day)), 16 (donepezil (10 mg/day))

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 4.94 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 4.19. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 19 total number of patients who suffered an adverse event of weight decrease before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 19 total number of patients who suffered an adverse event of weight decrease before end of treatment at 24 weeks

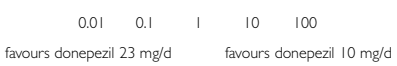
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	45/963	12/471		88.3 %	1.88 [0.98, 3.58]
Homma 2016	7/185	2/166		11.7 %	3.22 [0.66, 15.75]
Total (95% CI)	**1148**	**637**		**100.0 %**	**2.03 [1.12, 3.70]**

Total events: 52 (donepezil (23 mg/day)), 14 (donepezil (10 mg/day))

Heterogeneity: $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 2.32 (P = 0.020)

Test for subgroup differences: Not applicable



Analysis 4.20. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 20 total number of patients who suffered an adverse event of accidental fall before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 20 total number of patients who suffered an adverse event of accidental fall before end of treatment at 24 weeks

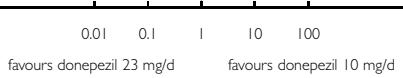
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	39/963	18/471		100.0 %	1.06 [0.60, 1.88]
Total (95% CI)	**963**	**471**		**100.0 %**	**1.06 [0.60, 1.88]**

Total events: 39 (donepezil (23 mg/day)), 18 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.21 (P = 0.84)

Test for subgroup differences: Not applicable



Analysis 4.21. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 21 total number of patients who suffered an adverse event of urinary tract infection before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 21 total number of patients who suffered an adverse event of urinary tract infection before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	42/963	19/471		100.0 %	1.08 [0.62, 1.89]
Total (95% CI)	**963**	**471**		**100.0 %**	**1.08 [0.62, 1.89]**

Total events: 42 (donepezil (23 mg/day)), 19 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable

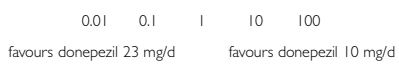
Analysis 4.22. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 22 total number of patients who suffered an adverse event of bradycardia and sinus bradycardia before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 22 total number of patients who suffered an adverse event of bradycardia and sinus bradycardia before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	27/963	3/471		100.0 %	4.50 [1.36, 14.91]
Total (95% CI)	**963**	**471**		**100.0 %**	**4.50 [1.36, 14.91]**
Total events: 27 (donepezil (23 mg/day)), 3 (donepezil (10 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.46 (P = 0.014)					
Test for subgroup differences: Not applicable					



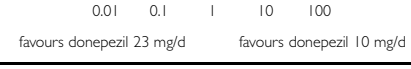
Analysis 4.23. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 23 total number of patients who suffered an adverse event of agitation before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 23 total number of patients who suffered an adverse event of agitation before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	38/963	18/471		100.0 %	1.03 [0.58, 1.83]
Total (95% CI)	**963**	**471**		**100.0 %**	**1.03 [0.58, 1.83]**
Total events: 38 (donepezil (23 mg/day)), 18 (donepezil (10 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.91)					
Test for subgroup differences: Not applicable					



Analysis 4.24. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 24 total number of patients who suffered an adverse event of aggression before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 24 total number of patients who suffered an adverse event of aggression before end of treatment at 24 weeks

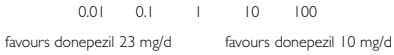
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	26/963	12/471		100.0 %	1.06 [0.53, 2.12]
Total (95% CI)	**963**	**471**		**100.0 %**	**1.06 [0.53, 2.12]**

Total events: 26 (donepezil (23 mg/day)), 12 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.17 (P = 0.87)

Test for subgroup differences: Not applicable



Analysis 4.25. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 25 total number of patients who suffered an adverse event of urinary incontinence before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 25 total number of patients who suffered an adverse event of urinary incontinence before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	24/963	6/471		100.0 %	1.98 [0.80, 4.88]
Total (95% CI)	**963**	**471**		**100.0 %**	**1.98 [0.80, 4.88]**

Total events: 24 (donepezil (23 mg/day)), 6 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 1.49 (P = 0.14)

Test for subgroup differences: Not applicable

Analysis 4.26. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 26 total number of patients who suffered an adverse event of somnolence before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 26 total number of patients who suffered an adverse event of somnolence before end of treatment at 24 weeks

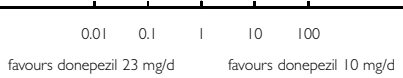
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	20/963	5/471		92.7 %	1.98 [0.74, 5.30]
Homma 2016	4/185	0/166		7.3 %	8.26 [0.44, 154.51]
Total (95% CI)	**1148**	**637**		**100.0 %**	**2.43 [0.97, 6.12]**

Total events: 24 (donepezil (23 mg/day)), 5 (donepezil (10 mg/day))

Heterogeneity: Chi^2 = 0.84, df = 1 (P = 0.36); I^2 =0.0%

Test for overall effect: Z = 1.89 (P = 0.059)

Test for subgroup differences: Not applicable



Analysis 4.27. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 27 total number of patients who died before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 27 total number of patients who died before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Farlow 2010	8/963	5/471		80.9 %	0.78 [0.25, 2.40]
Homma 2016	0/185	1/166		19.1 %	0.30 [0.01, 7.35]
Total (95% CI)	**1148**	**637**		**100.0 %**	**0.69 [0.24, 1.95]**

Total events: 8 (donepezil (23 mg/day)), 6 (donepezil (10 mg/day))

Heterogeneity: $Chi^2 = 0.31$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 0.70 (P = 0.48)

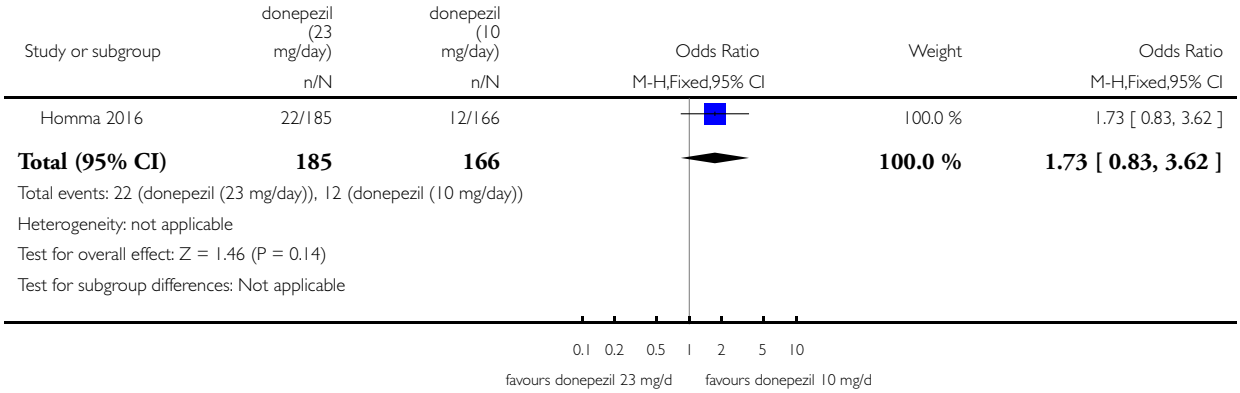
Test for subgroup differences: Not applicable

Analysis 4.28. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 28 total number of patients who suffered an adverse event of nasopharyngitis before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 28 total number of patients who suffered an adverse event of nasopharyngitis before end of treatment at 24 weeks

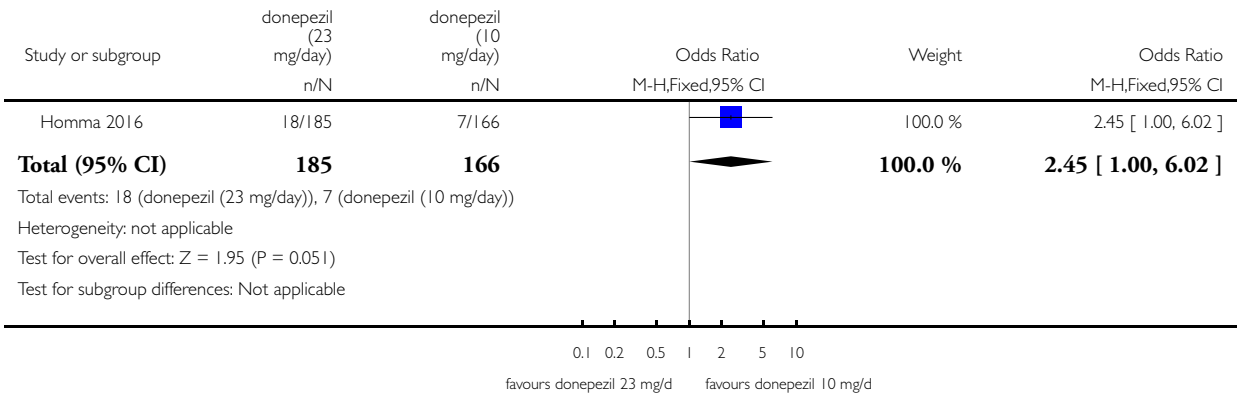


Analysis 4.29. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 29 total number of patients who suffered an adverse event of decreased appetite before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 29 total number of patients who suffered an adverse event of decreased appetite before end of treatment at 24 weeks



Analysis 4.30. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 30 total number of patients who suffered an adverse event of ECG QT prolonged before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 30 total number of patients who suffered an adverse event of ECG QT prolonged before end of treatment at 24 weeks

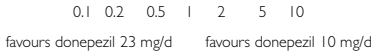
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	7/185	5/166		100.0 %	1.27 [0.39, 4.07]
Total (95% CI)	**185**	**166**		**100.0 %**	**1.27 [0.39, 4.07]**

Total events: 7 (donepezil (23 mg/day)), 5 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable



Analysis 4.31. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 31 total number of patients who suffered an adverse event of anger before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 31 total number of patients who suffered an adverse event of anger before end of treatment at 24 weeks

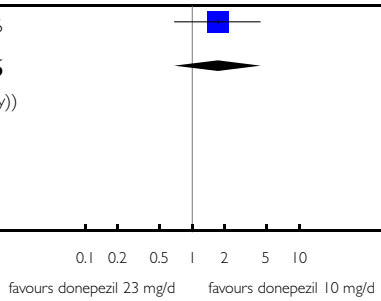
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	13/185	7/166		100.0 %	1.72 [0.67, 4.41]
Total (95% CI)	**185**	**166**		**100.0 %**	**1.72 [0.67, 4.41]**

Total events: 13 (donepezil (23 mg/day)), 7 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 1.12 (P = 0.26)

Test for subgroup differences: Not applicable



Analysis 4.32. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 32 total number of patients who suffered an adverse event of constipation before end of treatment at 24 weeks end of treatment.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 32 total number of patients who suffered an adverse event of constipation before end of treatment at 24 weeks end of treatment

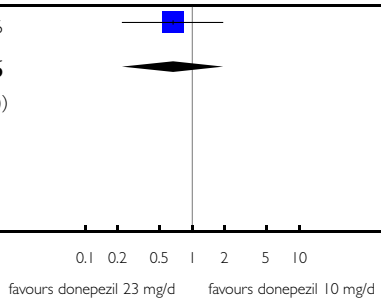
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	6/185	8/166		100.0 %	0.66 [0.22, 1.95]
Total (95% CI)	**185**	**166**		**100.0 %**	**0.66 [0.22, 1.95]**

Total events: 6 (donepezil (23 mg/day)), 8 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable



Analysis 4.33. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 33 total number of patients who suffered an adverse event of bronchitis before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 33 total number of patients who suffered an adverse event of bronchitis before end of treatment at 24 weeks

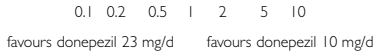
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	5/185	2/166		100.0 %	2.28 [0.44, 11.90]
Total (95% CI)	**185**	**166**		**100.0 %**	**2.28 [0.44, 11.90]**

Total events: 5 (donepezil (23 mg/day)), 2 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.98 (P = 0.33)

Test for subgroup differences: Not applicable



Analysis 4.34. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 34 total number of patients who suffered an adverse event of conjunctivitis before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 34 total number of patients who suffered an adverse event of conjunctivitis before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	5/185	0/166		100.0 %	10.15 [0.56, 184.91]
Total (95% CI)	**185**	**166**		**100.0 %**	**10.15 [0.56, 184.91]**
Total events: 5 (donepezil (23 mg/day)), 0 (donepezil (10 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.56 (P = 0.12)					
Test for subgroup differences: Not applicable					

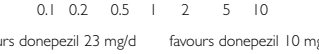
Analysis 4.35. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 35 total number of patients who suffered an adverse event of upper respiratory tract infection before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 35 total number of patients who suffered an adverse event of upper respiratory tract infection before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	4/185	3/166		100.0 %	1.20 [0.26, 5.45]
Total (95% CI)	**185**	**166**		**100.0 %**	**1.20 [0.26, 5.45]**
Total events: 4 (donepezil (23 mg/day)), 3 (donepezil (10 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.24 (P = 0.81)					
Test for subgroup differences: Not applicable					



Analysis 4.36. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 36 total number of patients who suffered an adverse event of arthralgia before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 36 total number of patients who suffered an adverse event of arthralgia before end of treatment at 24 weeks

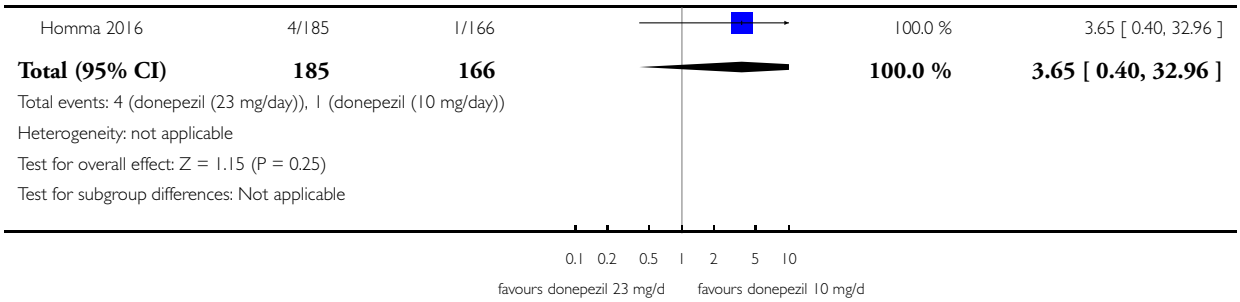
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	4/185	1/166		100.0 %	3.65 [0.40, 32.96]
Total (95% CI)	**185**	**166**		**100.0 %**	**3.65 [0.40, 32.96]**

Total events: 4 (donepezil (23 mg/day)), 1 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 1.15 (P = 0.25)

Test for subgroup differences: Not applicable



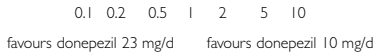
Analysis 4.37. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 37 total number of patients who suffered an adverse event of back pain before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 37 total number of patients who suffered an adverse event of back pain before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	4/185	2/166		100.0 %	1.81 [0.33, 10.02]
Total (95% CI)	**185**	**166**		**100.0 %**	**1.81 [0.33, 10.02]**
Total events: 4 (donepezil (23 mg/day)), 2 (donepezil (10 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: Not applicable					



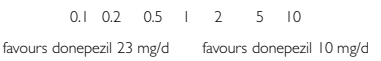
Analysis 4.38. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 38 total number of patients who suffered an adverse event of spinal compression fracture before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 38 total number of patients who suffered an adverse event of spinal compression fracture before end of treatment at 24 weeks

Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	4/185	0/166		100.0 %	8.26 [0.44, 154.51]
Total (95% CI)	**185**	**166**		**100.0 %**	**8.26 [0.44, 154.51]**
Total events: 4 (donepezil (23 mg/day)), 0 (donepezil (10 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					
Test for subgroup differences: Not applicable					



Analysis 4.39. Comparison 4 Donepezil (23 mg/day) versus donepezil (10 mg/day), Outcome 39 total number of patients who suffered an adverse event of dermatitis contact before end of treatment at 24 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 4 Donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome: 39 total number of patients who suffered an adverse event of dermatitis contact before end of treatment at 24 weeks

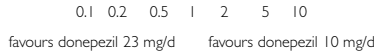
Study or subgroup	donepezil (23 mg/day) n/N	donepezil (10 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2016	2/185	4/166		100.0 %	0.44 [0.08, 2.45]
Total (95% CI)	**185**	**166**		**100.0 %**	**0.44 [0.08, 2.45]**

Total events: 2 (donepezil (23 mg/day)), 4 (donepezil (10 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.93 (P = 0.35)

Test for subgroup differences: Not applicable



Analysis 5.1. Comparison 5 Donepezil (15-20 mg/day) versus donepezil (10 mg/day), Outcome 1 Number who suffered an adverse event before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 5 Donepezil (15-20 mg/day) versus donepezil (10 mg/day)

Outcome: 1 Number who suffered an adverse event before end of treatment at 26 weeks

Study or subgroup	donepezil15-20 mg/d n/N	donepezil 10 mg/day n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Schindler 2004	6/16	4/15		100.0 %	1.65 [0.36, 7.60]
Total (95% CI)	**16**	**15**		**100.0 %**	**1.65 [0.36, 7.60]**

Total events: 6 (donepezil15-20 mg/d), 4 (donepezil 10 mg/day)

Heterogeneity: not applicable

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable

Analysis 6.1. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 1 CMAI (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 1 CMAI (change from baseline) completers

Study or subgroup	donepezil N	placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Howard 2007	113	108	0.18 (2.25)		100.0 %	0.18 [-4.23, 4.59]
Total (95% CI)	**113**	**108**			**100.0 %**	**0.18 [-4.23, 4.59]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.08 (P = 0.94)

Test for subgroup differences: Not applicable

Analysis 6.2. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 2 NPI (change from baseline) completers.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 2 NPI (change from baseline) completers

Study or subgroup	donepezil N	placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Howard 2007	104	97	0.1 (1.98)		100.0 %	0.10 [-3.78, 3.98]
Total (95% CI)	**104**	**97**			**100.0 %**	**0.10 [-3.78, 3.98]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable

Analysis 6.3. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 3 NPI caregiver distress (change from baseline).

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 3 NPI caregiver distress (change from baseline)

Study or subgroup	donepezil N	placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Howard 2007	105	95	-0.45 (0.82)		100.0 %	-0.45 [-2.06, 1.16]
Total (95% CI)	**105**	**95**			**100.0 %**	**-0.45 [-2.06, 1.16]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.55 (P = 0.58)

Test for subgroup differences: Not applicable

Analysis 6.4. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 4 Total number of withdrawals before end of treatment.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 4 Total number of withdrawals before end of treatment

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	13/128	19/131		100.0 %	0.67 [0.31, 1.41]
Total (95% CI)	**128**	**131**		**100.0 %**	**0.67 [0.31, 1.41]**
Total events: 13 (donepezil), 19 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					
Test for subgroup differences: Not applicable					

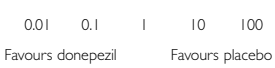
Analysis 6.5. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 5 Total number of participants who suffered from nausea.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 5 Total number of participants who suffered from nausea

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	3/128	1/131		100.0 %	3.12 [0.32, 30.40]
Total (95% CI)	**128**	**131**		**100.0 %**	**3.12 [0.32, 30.40]**
Total events: 3 (donepezil), 1 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Not applicable					



Analysis 6.6. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 6 Total number of participants who suffered from diarrhoea.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 6 Total number of participants who suffered from diarrhoea

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	2/128	0/131		100.0 %	5.20 [0.25, 109.33]
Total (95% CI)	**128**	**131**		**100.0 %**	**5.20 [0.25, 109.33]**

Total events: 2 (donepezil), 0 (placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable

Analysis 6.7. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 7 Total number of participants who suffered from rash.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 7 Total number of participants who suffered from rash

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	2/128	1/131		100.0 %	2.06 [0.18, 23.04]
Total (95% CI)	**128**	**131**		**100.0 %**	**2.06 [0.18, 23.04]**

Total events: 2 (donepezil), 1 (placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable

Analysis 6.8. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 8 Total number of participants who suffered from increased agitation.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 8 Total number of participants who suffered from increased agitation

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	2/128	3/131		100.0 %	0.68 [0.11, 4.12]
Total (95% CI)	**128**	**131**		**100.0 %**	**0.68 [0.11, 4.12]**
Total events: 2 (donepezil), 3 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					
Test for subgroup differences: Not applicable					

Analysis 6.9. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 9 Total number of participants who suffered from postural hypotension.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 9 Total number of participants who suffered from postural hypotension

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	0/128	1/131		100.0 %	0.34 [0.01, 8.39]
Total (95% CI)	**128**	**131**		**100.0 %**	**0.34 [0.01, 8.39]**
Total events: 0 (donepezil), 1 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Test for subgroup differences: Not applicable					

Analysis 6.10. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 10 Total number of participants who suffered from a fall.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 10 Total number of participants who suffered from a fall

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	2/128	2/131		100.0 %	1.02 [0.14, 7.38]
Total (95% CI)	**128**	**131**		**100.0 %**	**1.02 [0.14, 7.38]**
Total events: 2 (donepezil), 2 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
Test for subgroup differences: Not applicable					

Analysis 6.11. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 11 Total number of participants who suffered from femoral fracture.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 11 Total number of participants who suffered from femoral fracture

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	2/128	0/131		100.0 %	5.20 [0.25, 109.33]
Total (95% CI)	**128**	**131**		**100.0 %**	**5.20 [0.25, 109.33]**
Total events: 2 (donepezil), 0 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					
Test for subgroup differences: Not applicable					

Analysis 6.12. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 12 Total number of participants who suffered from a stroke.

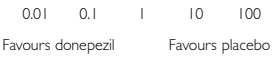
Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 12 Total number of participants who suffered from a stroke

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	1/128	0/131		100.0 %	3.09 [0.12, 76.66]
Total (95% CI)	**128**	**131**		**100.0 %**	**3.09 [0.12, 76.66]**

Total events: 1 (donepezil), 0 (placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 6.13. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 13 Total number of participants who suffered from myocardial infarct.

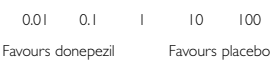
Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 13 Total number of participants who suffered from myocardial infarct

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	1/128	0/131		100.0 %	3.09 [0.12, 76.66]
Total (95% CI)	**128**	**131**		**100.0 %**	**3.09 [0.12, 76.66]**

Total events: 1 (donepezil), 0 (placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 6.14. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 14 Total number of participants who suffered from urinary tract infection.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 14 Total number of participants who suffered from urinary tract infection

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	2/128	3/131		100.0 %	0.68 [0.11, 4.12]
Total (95% CI)	**128**	**131**		**100.0 %**	**0.68 [0.11, 4.12]**
Total events: 2 (donepezil), 3 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					
Test for subgroup differences: Not applicable					

Analysis 6.15. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 15 Total number of participants who suffered from chest infection.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 15 Total number of participants who suffered from chest infection

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	1/128	1/131		100.0 %	1.02 [0.06, 16.54]
Total (95% CI)	**128**	**131**		**100.0 %**	**1.02 [0.06, 16.54]**
Total events: 1 (donepezil), 1 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.99)					
Test for subgroup differences: Not applicable					

Analysis 6.16. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 16 Total number of participants who suffered from seizure.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 16 Total number of participants who suffered from seizure

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	2/128	3/131		100.0 %	0.68 [0.11, 4.12]
Total (95% CI)	**128**	**131**		**100.0 %**	**0.68 [0.11, 4.12]**
Total events: 2 (donepezil), 3 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					
Test for subgroup differences: Not applicable					

Analysis 6.17. Comparison 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation, Outcome 17 Total number of deaths.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 6 Donepezil (10 mg/day) versus placebo at 12 weeks for people with AD with severe agitation

Outcome: 17 Total number of deaths

Study or subgroup	donepezil n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Howard 2007	3/128	4/131		100.0 %	0.76 [0.17, 3.47]
Total (95% CI)	**128**	**131**		**100.0 %**	**0.76 [0.17, 3.47]**
Total events: 3 (donepezil), 4 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.35 (P = 0.73)					
Test for subgroup differences: Not applicable					

Analysis 7.1. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 1 ADAS-Cog (change from baseline at 24 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

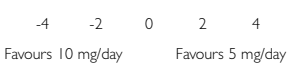
Outcome: 1 ADAS-Cog (change from baseline at 24 weeks) ITT-LOCF

Study or subgroup	donepezil (10 mg/day) N	Mean(SD)	donepezil (5 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Burns 1999	254	-1.26 (5.5)	262	0.18 (5.5)		62.4 %	-1.44 [-2.39, -0.49]
Rogers 1998b	150	-1.06 (5.42)	152	-0.67 (5.43)		37.6 %	-0.39 [-1.61, 0.83]
Total (95% CI)	**404**		**414**			**100.0 %**	**-1.05 [-1.80, -0.30]**

Heterogeneity: Chi^2 = 1.77, df = 1 (P = 0.18); I^2 =43%

Test for overall effect: Z = 2.73 (P = 0.0063)

Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 2 MMSE (change from baseline at 24 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 2 MMSE (change from baseline at 24 weeks) ITT-LOCF

Study or subgroup	donepezil (10 mg/day) N	Mean(SD)	donepezil (5 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Rogers 1998b	150	0.39 (3.1)	153	0.24 (3.1)		100.0 %	0.15 [-0.55, 0.85]
Total (95% CI)	**150**		**153**			**100.0 %**	**0.15 [-0.55, 0.85]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.42 (P = 0.67)

Test for subgroup differences: Not applicable

Analysis 7.3. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 3 SIB (change from baseline) at 24 weeks ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 3 SIB (change from baseline) at 24 weeks ITT-LOCF

Study or subgroup	donepezil (10 mg/day) N	Mean(SD)	donepezil (5 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Homma 2008	92	4.7 (11.2)	96	2.5 (11.2)		100.0 %	2.20 [-1.00, 5.40]
Total (95% CI)	**92**		**96**			**100.0 %**	**2.20 [-1.00, 5.40]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.35 (P = 0.18)

Test for subgroup differences: Not applicable

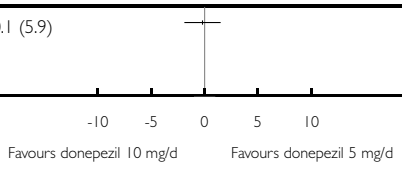
Analysis 7.4. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 4 ADCS-ADL-sev (change from baseline) at 24 weeks ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 4 ADCS-ADL-sev (change from baseline) at 24 weeks ITT-LOCF

Study or subgroup	donepezil (10 mg/day) N	Mean(SD)	donepezil (5 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Homma 2008	92	-0.3 (5.8)	96	-0.1 (5.9)			-0.20 [-1.87, 1.47]



Analysis 7.5. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 5 CIBIC-plus (numbers improved) by end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 5 CIBIC-plus (numbers improved) by end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	60/241	53/254		46.0 %	1.26 [0.83, 1.91]
Homma 2008	43/92	31/96		19.2 %	1.84 [1.02, 3.33]
Rogers 1998b	37/149	39/149		34.8 %	0.93 [0.55, 1.57]
Total (95% CI)	**482**	**499**		**100.0 %**	**1.26 [0.94, 1.67]**

Total events: 140 (donepezil (10 mg/day)), 123 (donepezil (5 mg/day))

Heterogeneity: $Chi^2 = 2.86$, df = 2 (P = 0.24); $I^2 = 30\%$

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable

Analysis 7.6. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 6 CDR-SB (change from baseline at 24 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 6 CDR-SB (change from baseline at 24 weeks) ITT-LOCF

Study or subgroup	donepezil (10 mg/day) N	Mean(SD)	donepezil (5 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Burns 1999	258	-0.06 (1.6)	261	0.06 (1.6)		60.6 %	-0.12 [-0.40, 0.16]
Rogers 1998b	151	-0.02 (1.52)	154	-0.01 (1.52)		39.4 %	-0.01 [-0.35, 0.33]
Total (95% CI)	**409**		**415**			**100.0 %**	**-0.08 [-0.29, 0.14]**

Heterogeneity: $Chi^2 = 0.24$, df = 1 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.70 (P = 0.48)

Test for subgroup differences: Not applicable

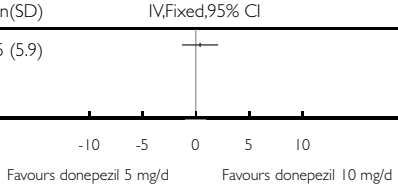
Analysis 7.7. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 7 BEHAVE-AD (change from baseline) at 24 weeks ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 7 BEHAVE-AD (change from baseline) at 24 weeks ITT-LOCF

Study or subgroup	donepezil (10 mg/day) N	Mean(SD)	donepezil (5 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Homma 2008	92	-0.1 (5.8)	96	-0.5 (5.9)			0.40 [-1.27, 2.07]



Analysis 7.8. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 8 QoL (change from baseline at 24 weeks) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 8 QoL (change from baseline at 24 weeks) ITT-LOCF

Study or subgroup	donepezil (10 mg/day) N	Mean(SD)	donepezil (5 mg/day) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Rogers 1998b	150	-4.88 (35)	152	3.45 (35)		100.0 %	-8.33 [-16.23, -0.43]
Total (95% CI)	**150**		**152**			**100.0 %**	**-8.33 [-16.23, -0.43]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.07 (P = 0.039)

Test for subgroup differences: Not applicable

Analysis 7.9. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 9 Total number of participants who withdrew before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 9 Total number of participants who withdrew before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	72/273	60/271		63.3 %	1.26 [0.85, 1.87]
Homma 2008	20/96	13/101		14.3 %	1.78 [0.83, 3.82]
Rogers 1998b	51/157	23/154		22.4 %	2.74 [1.57, 4.77]
Total (95% CI)	**526**	**526**		**100.0 %**	**1.67 [1.24, 2.23]**

Total events: 143 (donepezil (10 mg/day)), 96 (donepezil (5 mg/day))

Heterogeneity: Chi^2 = 5.06, df = 2 (P = 0.08); I^2 =60%

Test for overall effect: Z = 3.41 (P = 0.00064)

Test for subgroup differences: Not applicable

Analysis 7.10. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 10 Total number of participants who withdrew due to an adverse event before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 10 Total number of participants who withdrew due to an adverse event before end of treatment at 26 weeks

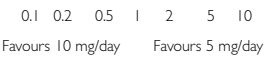
Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	50/273	24/271		57.9 %	2.31 [1.37, 3.88]
Homma 2008	13/96	8/101		19.8 %	1.82 [0.72, 4.61]
Rogers 1998b	26/157	9/154		22.3 %	3.20 [1.45, 7.07]
Total (95% CI)	**526**	**526**		**100.0 %**	**2.41 [1.63, 3.57]**

Total events: 89 (donepezil (10 mg/day)), 41 (donepezil (5 mg/day))

Heterogeneity: $Chi^2 = 0.86$, df = 2 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 4.39 (P = 0.000011)

Test for subgroup differences: Not applicable



Analysis 7.11. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 11 Total number of participants who suffered an adverse event before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 11 Total number of participants who suffered an adverse event before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	234/273	213/271		70.4 %	1.63 [1.05, 2.55]
Homma 2008	80/96	79/101		29.6 %	1.39 [0.68, 2.85]
Total (95% CI)	**369**	**372**		**100.0 %**	**1.56 [1.07, 2.28]**

Total events: 314 (donepezil (10 mg/day)), 292 (donepezil (5 mg/day))

Heterogeneity: $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 2.31 (P = 0.021)

Test for subgroup differences: Not applicable

Analysis 7.12. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 12 Total number of participants who suffered an adverse event of anorexia before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 12 Total number of participants who suffered an adverse event of anorexia before end of treatment at 26 weeks

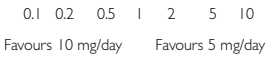
Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	21/273	11/271		73.3 %	1.97 [0.93, 4.17]
Homma 2008	7/96	1/101		6.5 %	7.87 [0.95, 65.18]
Rogers 1998b	11/157	3/154		20.2 %	3.79 [1.04, 13.87]
Total (95% CI)	**526**	**526**		**100.0 %**	**2.72 [1.48, 5.00]**

Total events: 39 (donepezil (10 mg/day)), 15 (donepezil (5 mg/day))

Heterogeneity: Chi^2 = 1.93, df = 2 (P = 0.38); I^2 =0.0%

Test for overall effect: Z = 3.22 (P = 0.0013)

Test for subgroup differences: Not applicable



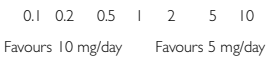
Analysis 7.13. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 13 Total number of participants who suffered an adverse event of confusion before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 13 Total number of participants who suffered an adverse event of confusion before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	16/274	19/271		100.0 %	0.82 [0.41, 1.64]
Total (95% CI)	**274**	**271**		**100.0 %**	**0.82 [0.41, 1.64]**
Total events: 16 (donepezil (10 mg/day)), 19 (donepezil (5 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.58)					
Test for subgroup differences: Not applicable					



Analysis 7.14. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 14 Total number of participants who suffered an adverse event of diarrhoea before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 14 Total number of participants who suffered an adverse event of diarrhoea before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	45/273	28/271		57.9 %	1.71 [1.03, 2.84]
Homma 2008	8/96	6/101		13.2 %	1.44 [0.48, 4.31]
Rogers 1998b	27/157	14/154		28.9 %	2.08 [1.04, 4.13]
Total (95% CI)	**526**	**526**		**100.0 %**	**1.78 [1.22, 2.61]**
Total events: 80 (donepezil (10 mg/day)), 48 (donepezil (5 mg/day))					
Heterogeneity: Chi^2 = 0.36, df = 2 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 2.97 (P = 0.0030)					
Test for subgroup differences: Not applicable					

Analysis 7.15. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 15 Total number of participants who suffered an adverse event of dizziness before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 15 Total number of participants who suffered an adverse event of dizziness before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	25/273	13/271		46.0 %	2.00 [1.00, 4.00]
Rogers 1998b	13/157	15/154		54.0 %	0.84 [0.38, 1.82]
Total (95% CI)	**430**	**425**		**100.0 %**	**1.37 [0.83, 2.28]**

Total events: 38 (donepezil (10 mg/day)), 28 (donepezil (5 mg/day))

Heterogeneity: $Chi^2 = 2.69$, df = 1 (P = 0.10); $I^2 = 63\%$

Test for overall effect: Z = 1.22 (P = 0.22)

Test for subgroup differences: Not applicable

Analysis 7.16. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 16 Total number of participants who suffered an adverse event of fatigue before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 16 Total number of participants who suffered an adverse event of fatigue before end of treatment at 26 weeks

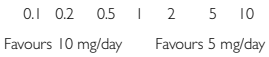
Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Rogers 1998b	12/157	8/154		100.0 %	1.51 [0.60, 3.80]
Total (95% CI)	**157**	**154**		**100.0 %**	**1.51 [0.60, 3.80]**

Total events: 12 (donepezil (10 mg/day)), 8 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.87 (P = 0.38)

Test for subgroup differences: Not applicable



Analysis 7.17. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 17 Total number of participants who suffered an adverse event of headache before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 17 Total number of participants who suffered an adverse event of headache before end of treatment at 26 weeks

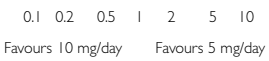
Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	39/274	33/271		100.0 %	1.20 [0.73, 1.97]
Total (95% CI)	**274**	**271**		**100.0 %**	**1.20 [0.73, 1.97]**

Total events: 39 (donepezil (10 mg/day)), 33 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.71 (P = 0.48)

Test for subgroup differences: Not applicable



Analysis 7.18. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 18 Total number of participants who suffered an adverse event of insomnia before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 18 Total number of participants who suffered an adverse event of insomnia before end of treatment at 26 weeks

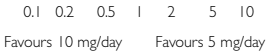
Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	22/274	19/271		100.0 %	1.16 [0.61, 2.19]
Total (95% CI)	**274**	**271**		**100.0 %**	**1.16 [0.61, 2.19]**

Total events: 22 (donepezil (10 mg/day)), 19 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.45 (P = 0.65)

Test for subgroup differences: Not applicable



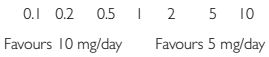
Analysis 7.19. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 19 Total number of participants who suffered an adverse event of muscle cramp before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 19 Total number of participants who suffered an adverse event of muscle cramp before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Rogers 1998b	12/157	9/154		100.0 %	1.33 [0.55, 3.26]
Total (95% CI)	**157**	**154**		**100.0 %**	**1.33 [0.55, 3.26]**
Total events: 12 (donepezil (10 mg/day)), 9 (donepezil (5 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
Test for subgroup differences: Not applicable					



Analysis 7.20. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 20 Total number of participants who suffered an adverse event of nausea before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 20 Total number of participants who suffered an adverse event of nausea before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	66/273	20/271		75.1 %	4.00 [2.35, 6.82]
Rogers 1998b	26/157	6/154		24.9 %	4.90 [1.95, 12.26]
Total (95% CI)	**430**	**425**		**100.0 %**	**4.22 [2.67, 6.70]**
Total events: 92 (donepezil (10 mg/day)), 26 (donepezil (5 mg/day))					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 6.13 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 7.21. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 21 Total number of participants who suffered an adverse event of rhinitis before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 21 Total number of participants who suffered an adverse event of rhinitis before end of treatment at 26 weeks

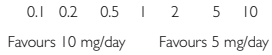
Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Rogers 1998b	9/157	1/154		100.0 %	9.30 [1.16, 74.35]
Total (95% CI)	**157**	**154**		**100.0 %**	**9.30 [1.16, 74.35]**

Total events: 9 (donepezil (10 mg/day)), 1 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 2.10 (P = 0.035)

Test for subgroup differences: Not applicable



Analysis 7.22. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 22 Total number of participants who suffered an adverse event of vomiting before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 22 Total number of participants who suffered an adverse event of vomiting before end of treatment at 26 weeks

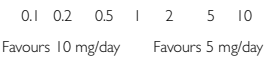
Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Burns 1999	43/273	12/271		49.5 %	4.04 [2.08, 7.84]
Homma 2008	14/96	7/101		28.4 %	2.29 [0.88, 5.95]
Rogers 1998b	16/157	5/154		22.1 %	3.38 [1.21, 9.47]
Total (95% CI)	**526**	**526**		**100.0 %**	**3.40 [2.10, 5.48]**

Total events: 73 (donepezil (10 mg/day)), 24 (donepezil (5 mg/day))

Heterogeneity: $Chi^2 = 0.91$, df = 2 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 5.00 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 7.23. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 23 Total number of participants who suffered an adverse event of cold syndrome before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 23 Total number of participants who suffered an adverse event of cold syndrome before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2008	18/96	19/101		100.0 %	1.00 [0.49, 2.04]
Total (95% CI)	**96**	**101**		**100.0 %**	**1.00 [0.49, 2.04]**
Total events: 18 (donepezil (10 mg/day)), 19 (donepezil (5 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
Test for subgroup differences: Not applicable					

Analysis 7.24. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 24 Total number of participants who suffered an adverse event of accidental fall before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 24 Total number of participants who suffered an adverse event of accidental fall before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2008	6/96	7/101		100.0 %	0.90 [0.29, 2.77]
Total (95% CI)	**96**	**101**		**100.0 %**	**0.90 [0.29, 2.77]**
Total events: 6 (donepezil (10 mg/day)), 7 (donepezil (5 mg/day))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.19 (P = 0.85)					
Test for subgroup differences: Not applicable					

Analysis 7.25. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 25 Total number of participants who suffered an adverse event of respiratory tract infection before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 25 Total number of participants who suffered an adverse event of respiratory tract infection before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2008	6/96	7/101		100.0 %	0.90 [0.29, 2.77]
Total (95% CI)	**96**	**101**		**100.0 %**	**0.90 [0.29, 2.77]**

Total events: 6 (donepezil (10 mg/day)), 7 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable

Analysis 7.26. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 26 Total number of participants who suffered an adverse event of constipation before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 26 Total number of participants who suffered an adverse event of constipation before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2008	5/96	8/101		100.0 %	0.64 [0.20, 2.03]
Total (95% CI)	**96**	**101**		**100.0 %**	**0.64 [0.20, 2.03]**

Total events: 5 (donepezil (10 mg/day)), 8 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable

Analysis 7.27. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 27 Total number of participants who suffered an adverse event of fever before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 27 Total number of participants who suffered an adverse event of fever before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2008	5/96	3/101		100.0 %	1.79 [0.42, 7.72]
Total (95% CI)	**96**	**101**		**100.0 %**	**1.79 [0.42, 7.72]**

Total events: 5 (donepezil (10 mg/day)), 3 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable

Analysis 7.28. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 28 Total number of participants who suffered an adverse event of loss of appetite before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 28 Total number of participants who suffered an adverse event of loss of appetite before end of treatment at 26 weeks

Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2008	4/96	5/101		100.0 %	0.83 [0.22, 3.21]
Total (95% CI)	**96**	**101**		**100.0 %**	**0.83 [0.22, 3.21]**

Total events: 4 (donepezil (10 mg/day)), 5 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.26 (P = 0.79)

Test for subgroup differences: Not applicable

Analysis 7.29. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 29 Total number of participants who suffered an adverse event of bruising before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 29 Total number of participants who suffered an adverse event of bruising before end of treatment at 26 weeks

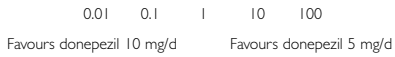
Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2008	3/96	5/101		100.0 %	0.62 [0.14, 2.67]
Total (95% CI)	**96**	**101**		**100.0 %**	**0.62 [0.14, 2.67]**

Total events: 3 (donepezil (10 mg/day)), 5 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable



Analysis 7.30. Comparison 7 Donepezil (10 mg/day) versus donepezil (5 mg/day), Outcome 30 Total number of participants who suffered an adverse event of restlessness before end of treatment at 26 weeks.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 7 Donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome: 30 Total number of participants who suffered an adverse event of restlessness before end of treatment at 26 weeks

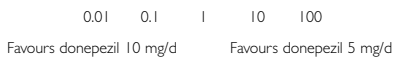
Study or subgroup	donepezil (10 mg/day) n/N	donepezil (5 mg/day) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Homma 2008	2/96	6/101		100.0 %	0.34 [0.07, 1.71]
Total (95% CI)	**96**	**101**		**100.0 %**	**0.34 [0.07, 1.71]**

Total events: 2 (donepezil (10 mg/day)), 6 (donepezil (5 mg/day))

Heterogeneity: not applicable

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable



Analysis 8.1. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 1 MMSE (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 1 MMSE (change from baseline) ITT-LOCF

Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (10 mg/d) at 24 weeks							
Black 2007	150	0.65 (3.31)	141	-0.03 (3.32)		28.8 %	0.68 [-0.08, 1.44]
Feldman 2001	131	1.35 (4.01)	139	-0.44 (3.99)		18.4 %	1.79 [0.84, 2.74]
Jia 2017	150	1.7 (3.3)	151	1 (3.44)		28.8 %	0.70 [-0.06, 1.46]
Winblad 2006	120	1.1 (3.3)	120	0.1 (3.3)		24.0 %	1.00 [0.17, 1.83]
Subtotal (95% CI)	**551**		**551**			**100.0 %**	**0.97 [0.56, 1.38]**
Heterogeneity: Chi^2 = 3.88, df = 3 (P = 0.28); I^2 =23%							
Test for overall effect: Z = 4.63 (P < 0.00001)							

Analysis 8.2. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 2 SIB (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 2 SIB (change from baseline) ITT-LOCF

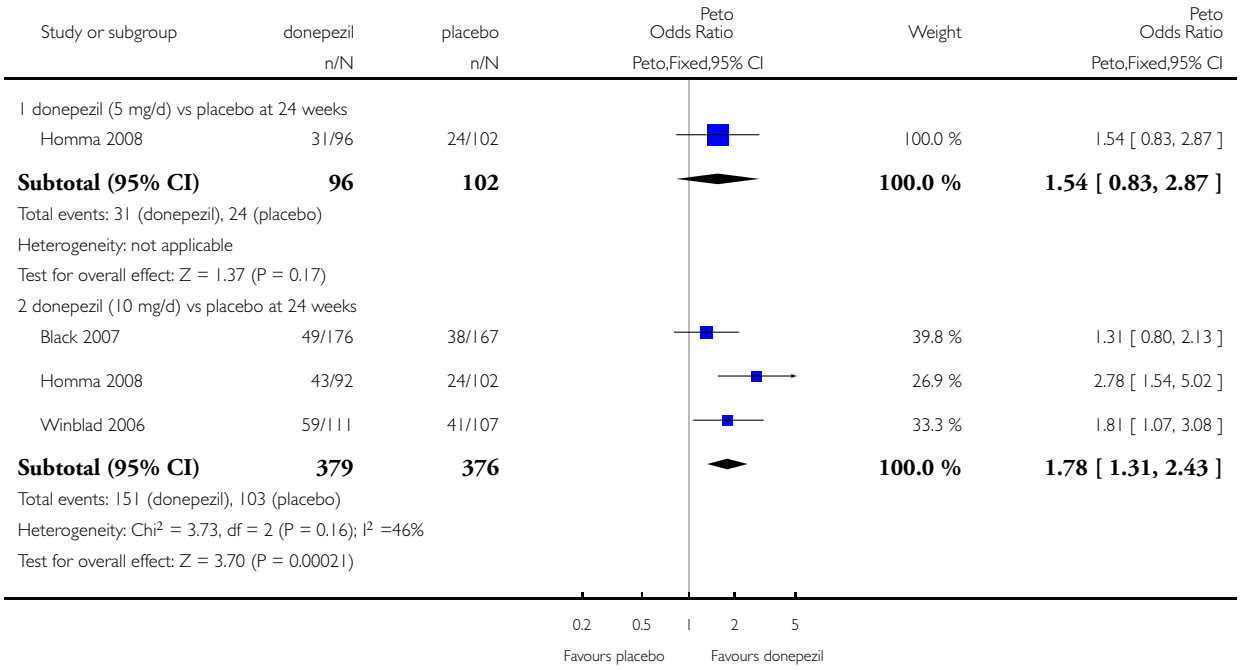
Study or subgroup	Donepezil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) at 24 weeks							
Homma 2008	96	2.5 (11.2)	102	-4.2 (10.6)		100.0 %	6.70 [3.66, 9.74]
Subtotal (95% CI)	**96**		**102**			**100.0 %**	**6.70 [3.66, 9.74]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.32 (P = 0.000016)							
2 donepezil (10 mg/d) at 24 weeks							
Black 2007	166	0.19 (12.5)	155	-5.13 (12.6)		25.7 %	5.32 [2.57, 8.07]
Feldman 2001	139	2.22 (13.1)	145	-3.56 (14.72)		18.5 %	5.78 [2.54, 9.02]
Homma 2008	92	4.7 (11.2)	102	-4.2 (10.6)		20.5 %	8.90 [5.82, 11.98]
Jia 2017	150	2.9 (14.45)	151	-2 (14.75)		17.8 %	4.90 [1.60, 8.20]
Winblad 2006	128	2.6 (13.6)	120	-1.9 (13.1)		17.6 %	4.50 [1.18, 7.82]
Subtotal (95% CI)	**675**		**673**			**100.0 %**	**5.92 [4.53, 7.31]**
Heterogeneity: Chi^2 = 4.86, df = 4 (P = 0.30); I^2 =18%							
Test for overall effect: Z = 8.33 (P < 0.00001)							

Analysis 8.3. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 3 CIBIC-Plus or CGIC (numbers improved) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 3 CIBIC-Plus or CGIC (numbers improved) ITT-LOCF



Analysis 8.4. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 4 ADCS-ADL-severe (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 4 ADCS-ADL-severe (change from baseline) ITT-LOCF

Study or subgroup	Donepezil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) at 24 weeks							
Homma 2008	96	-0.1 (5.9)	102	-1.1 (5.1)		100.0 %	1.00 [-0.54, 2.54]
Subtotal (95% CI)	**96**		**102**			**100.0 %**	**1.00 [-0.54, 2.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.27 (P = 0.20)							
2 donepezil (10 mg/d) at 24 weeks							
Black 2007	151	-1.82 (6.6)	140	-2.53 (6.6)		29.2 %	0.71 [-0.81, 2.23]
Homma 2008	92	-0.3 (5.8)	102	-1.1 (5.1)		28.2 %	0.80 [-0.74, 2.34]
Winblad 2006	128	-1.5 (4.5)	120	-2.9 (5.5)		42.6 %	1.40 [0.14, 2.66]
Subtotal (95% CI)	**371**		**362**			**100.0 %**	**1.03 [0.21, 1.85]**
Heterogeneity: Chi^2 = 0.59, df = 2 (P = 0.74); I^2 =0.0%							
Test for overall effect: Z = 2.46 (P = 0.014)							

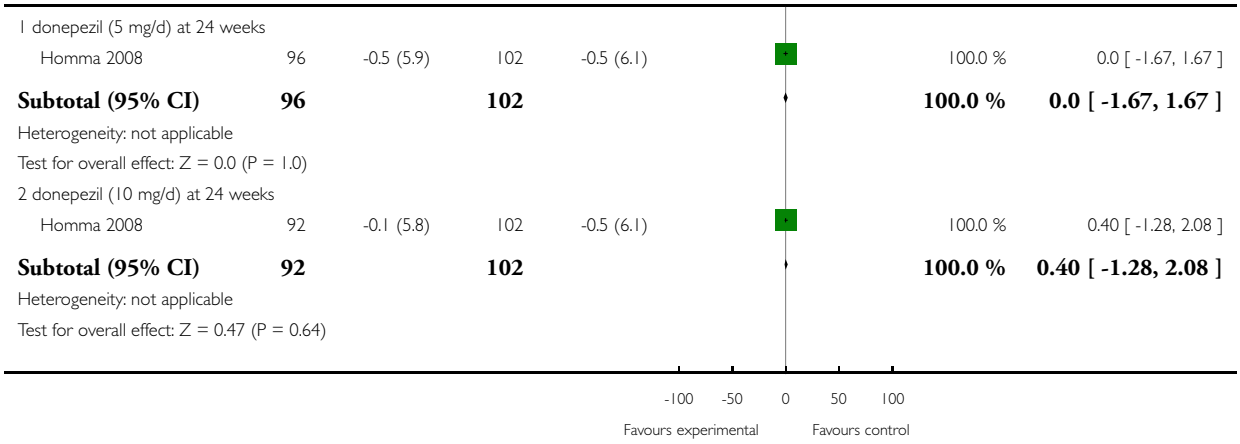
Analysis 8.5. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 5 BEHAVE-AD (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 5 BEHAVE-AD (change from baseline) ITT-LOCF

Study or subgroup	Donepezil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5 mg/d) at 24 weeks							
Homma 2008	96	-0.5 (5.9)	102	-0.5 (6.1)		100.0 %	0.0 [-1.67, 1.67]
Subtotal (95% CI)	**96**		**102**			**100.0 %**	**0.0 [-1.67, 1.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 donepezil (10 mg/d) at 24 weeks							
Homma 2008	92	-0.1 (5.8)	102	-0.5 (6.1)		100.0 %	0.40 [-1.28, 2.08]
Subtotal (95% CI)	**92**		**102**			**100.0 %**	**0.40 [-1.28, 2.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.47 (P = 0.64)							

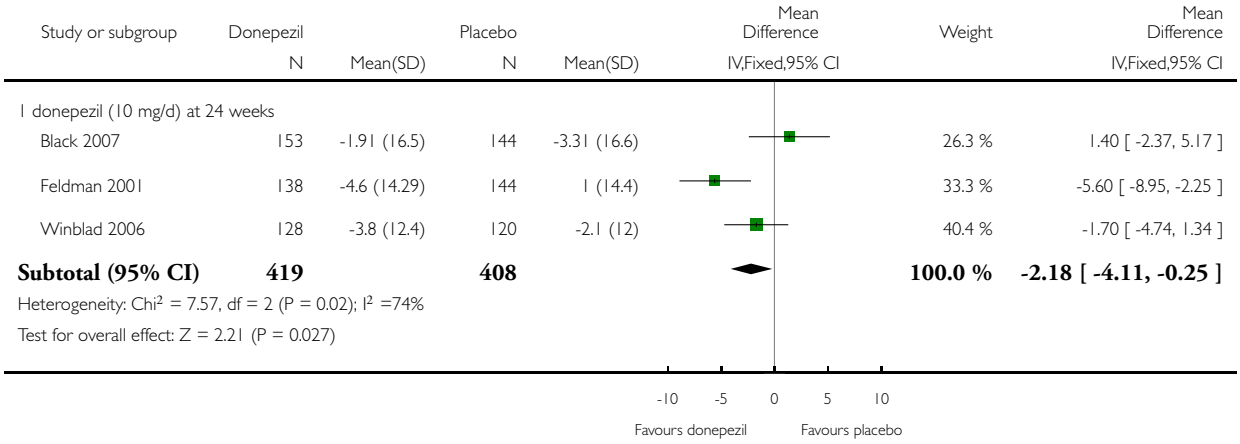


Analysis 8.6. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 6 Behavioural disturbance (total NPI) (change from baseline) ITT-LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 6 Behavioural disturbance (total NPI) (change from baseline) ITT-LOCF

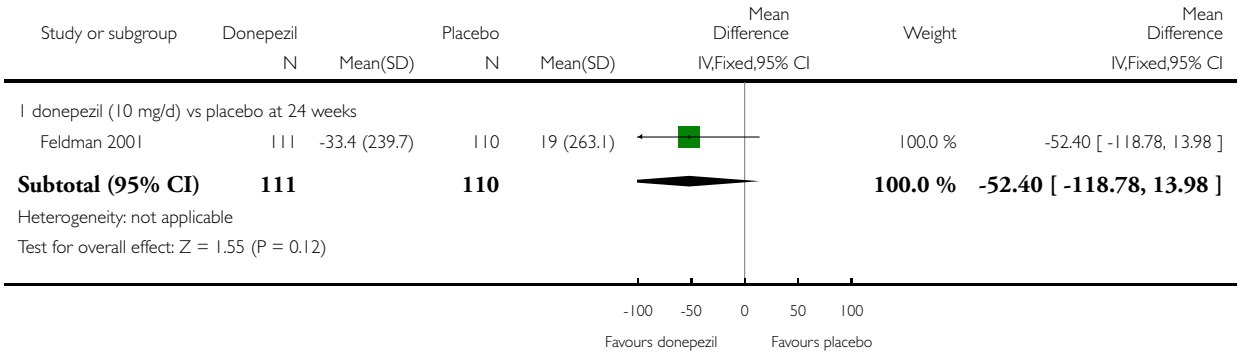


Analysis 8.7. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 7 Time (mins/day) spent by carer assisting in IADL and PSMS (change from baseline) LOCF.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 7 Time (mins/day) spent by carer assisting in IADL and PSMS (change from baseline) LOCF



Analysis 8.8. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 8 Total number of withdrawals before end of treatment.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 8 Total number of withdrawals before end of treatment

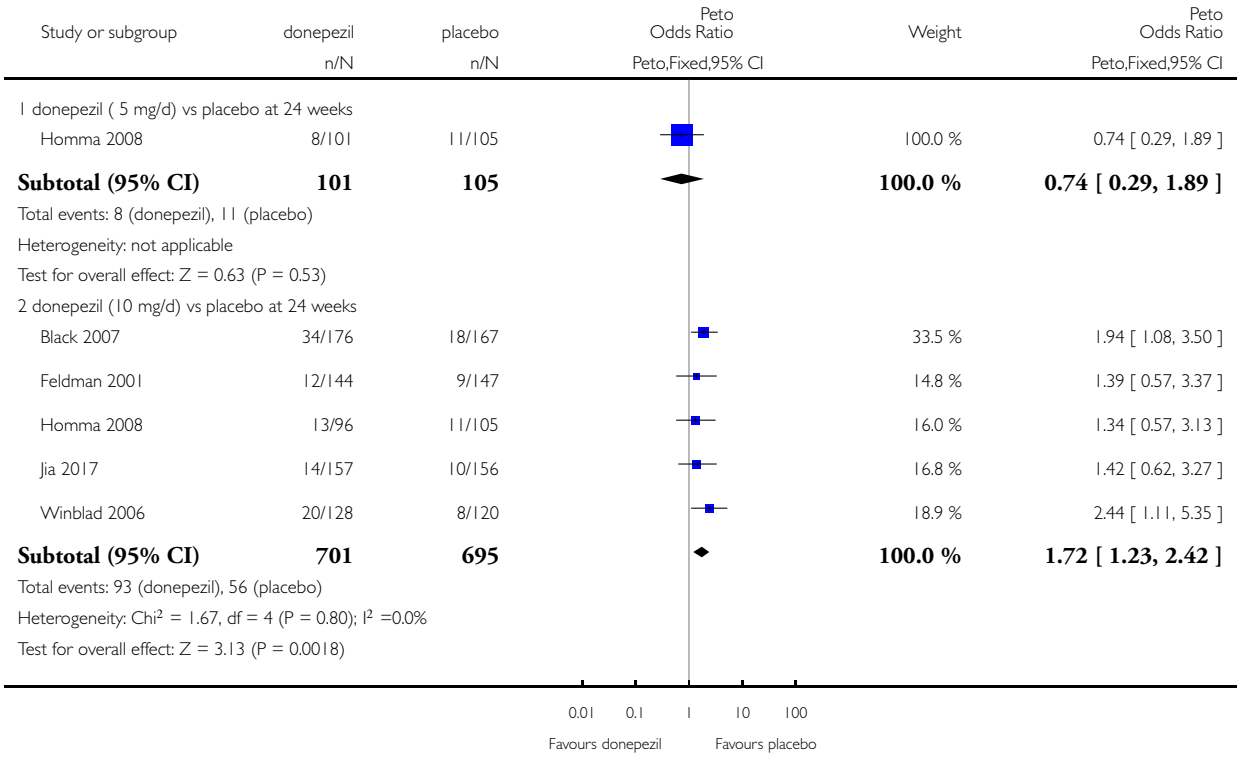
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 24 weeks					
Homma 2008	13/101	19/105		100.0 %	0.67 [0.32, 1.43]
Subtotal (95% CI)	**101**	**105**		**100.0 %**	**0.67 [0.32, 1.43]**
Total events: 13 (donepezil), 19 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
2 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	59/176	40/167		30.8 %	1.59 [1.00, 2.54]
Feldman 2001	23/144	20/147		16.0 %	1.21 [0.63, 2.30]
Homma 2008	20/96	19/105		13.8 %	1.19 [0.59, 2.39]
Jia 2017	29/157	30/156		20.9 %	0.95 [0.54, 1.68]
Winblad 2006	33/128	21/120		18.5 %	1.62 [0.89, 2.96]
Subtotal (95% CI)	**701**	**695**		**100.0 %**	**1.32 [1.02, 1.71]**
Total events: 164 (donepezil), 130 (placebo)					
Heterogeneity: Chi^2 = 2.51, df = 4 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 2.09 (P = 0.037)					
Test for subgroup differences: Chi^2 = 2.74, df = 1 (P = 0.10), I^2 =64%					

Analysis 8.9. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 9 Total number of participants who withdrew due to an adverse event.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 9 Total number of participants who withdrew due to an adverse event

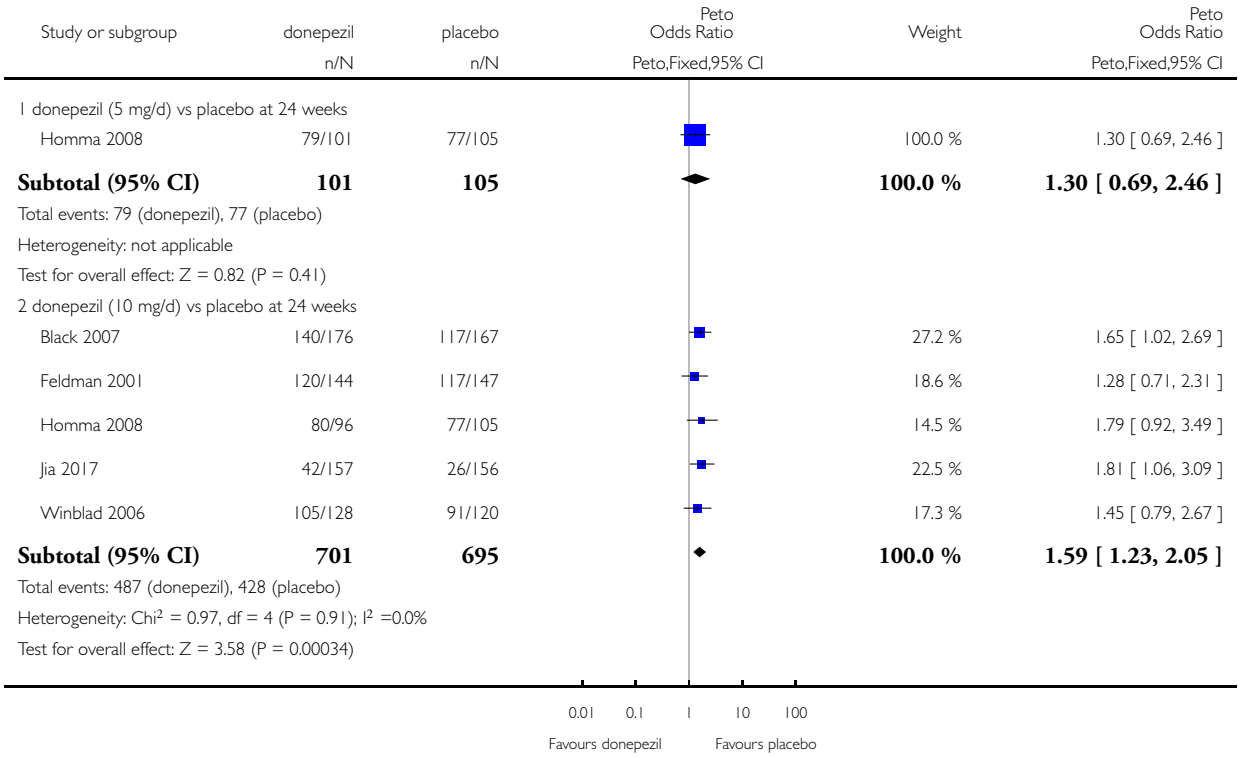


Analysis 8.10. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 10 Total number of participants who suffered from at least one adverse event.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 10 Total number of participants who suffered from at least one adverse event

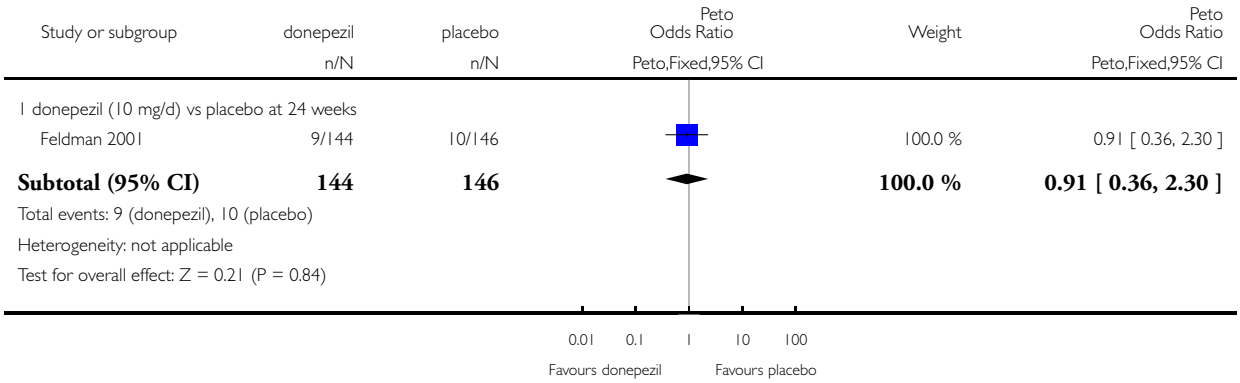


Analysis 8.11. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 11 Total number of participants who suffered from abdominal pain.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 11 Total number of participants who suffered from abdominal pain

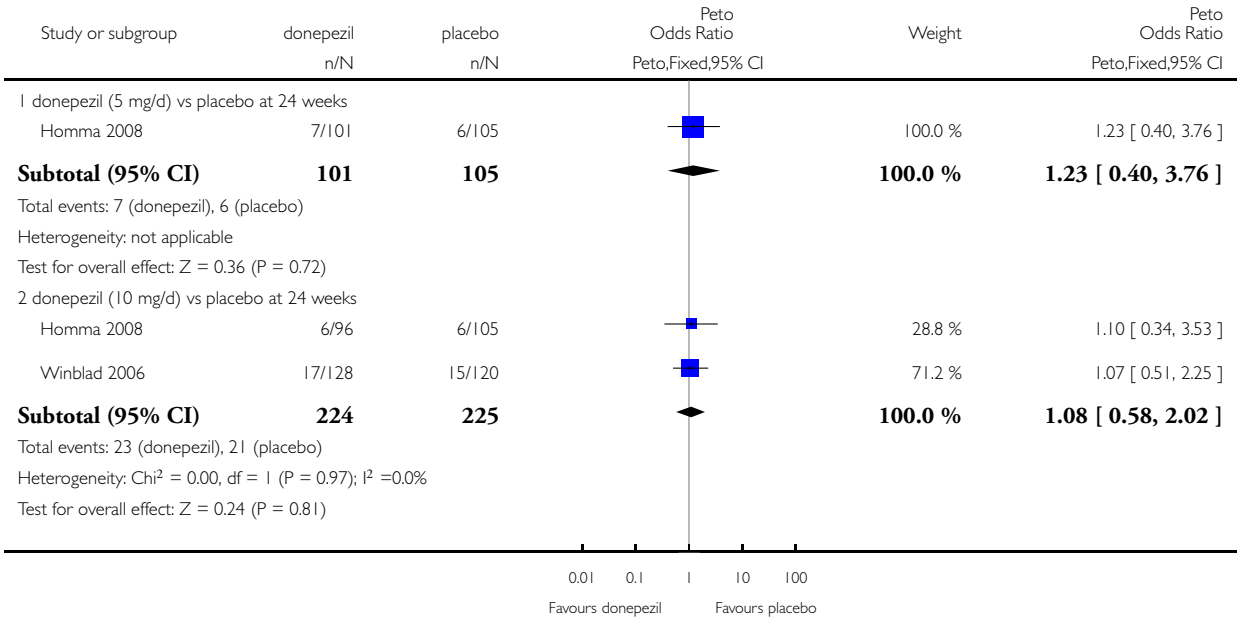


Analysis 8.12. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 12 Total number of participants who suffered from accidental fall.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 12 Total number of participants who suffered from accidental fall

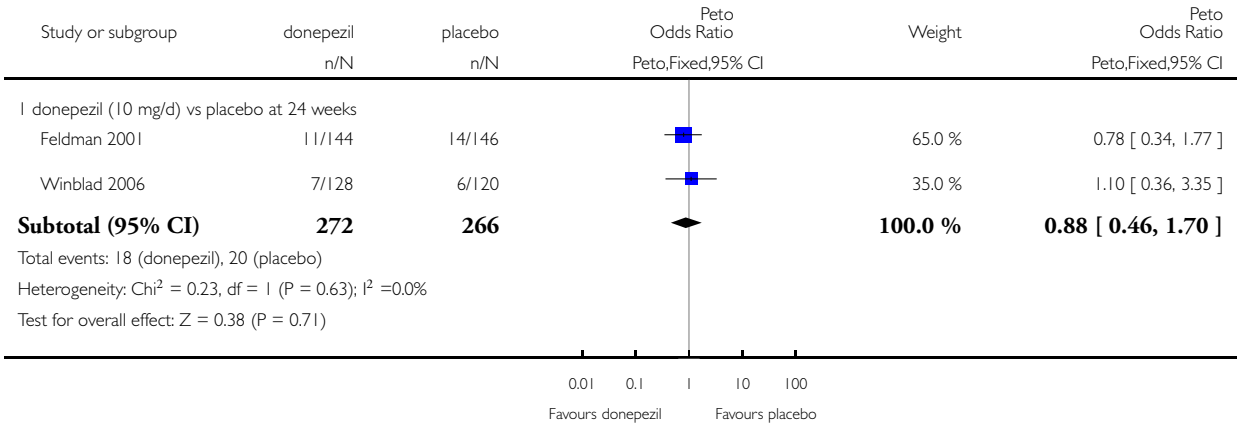


Analysis 8.13. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 13 Total number of participants who suffered from accidental injury.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 13 Total number of participants who suffered from accidental injury

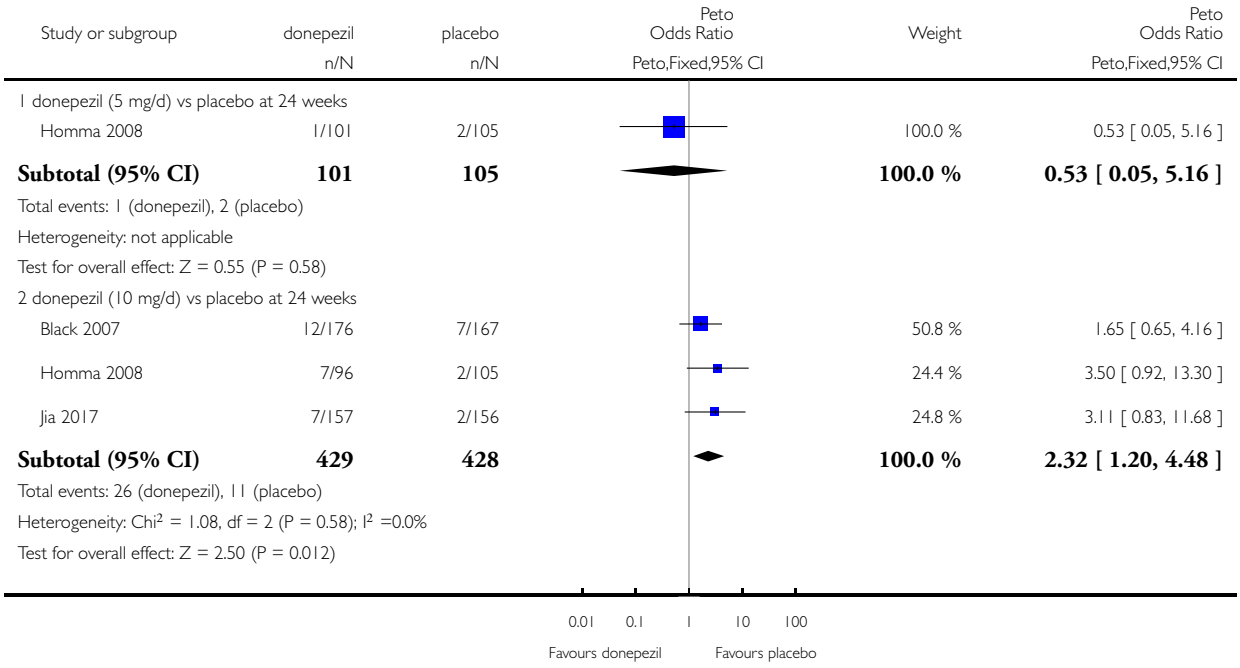


Analysis 8.14. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 14 Total number of participants who suffered from anorexia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 14 Total number of participants who suffered from anorexia

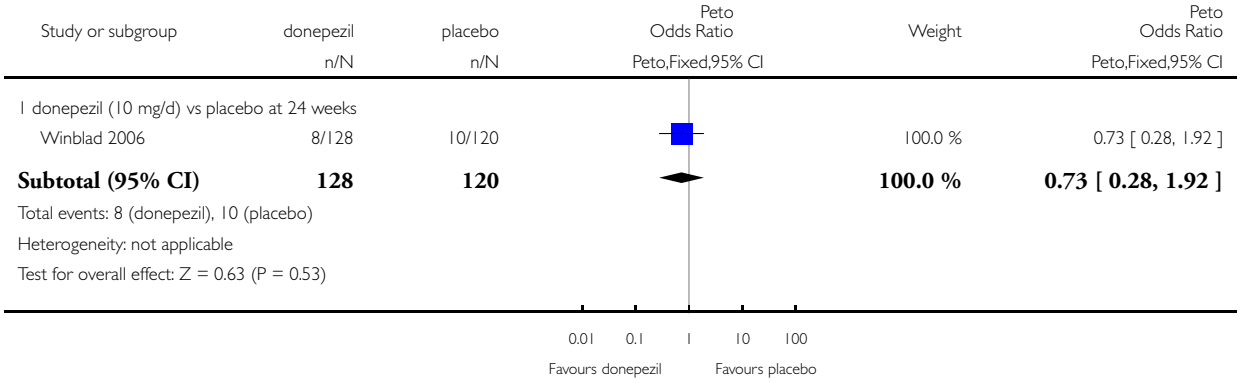


Analysis 8.15. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 15 Total number of participants who suffered from anxiety.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 15 Total number of participants who suffered from anxiety

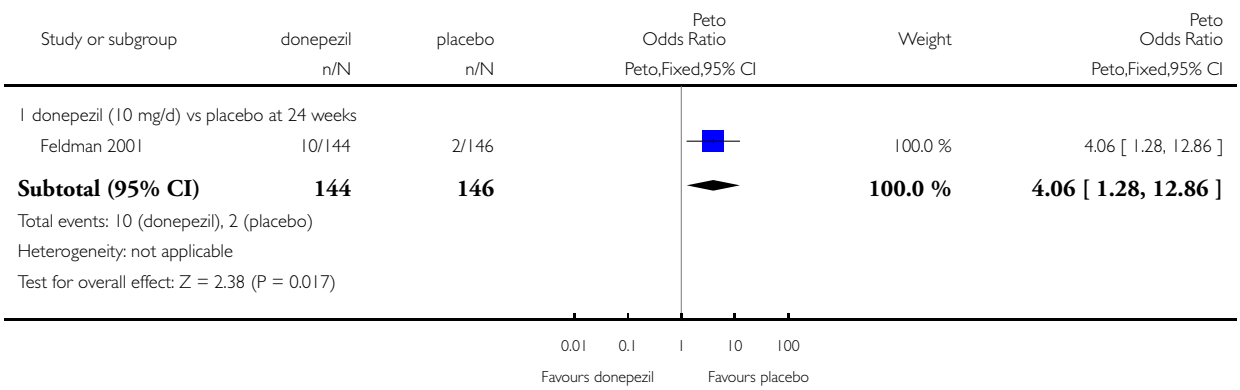


Analysis 8.16. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 16 Total number of participants who suffered from arthralgia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 16 Total number of participants who suffered from arthralgia

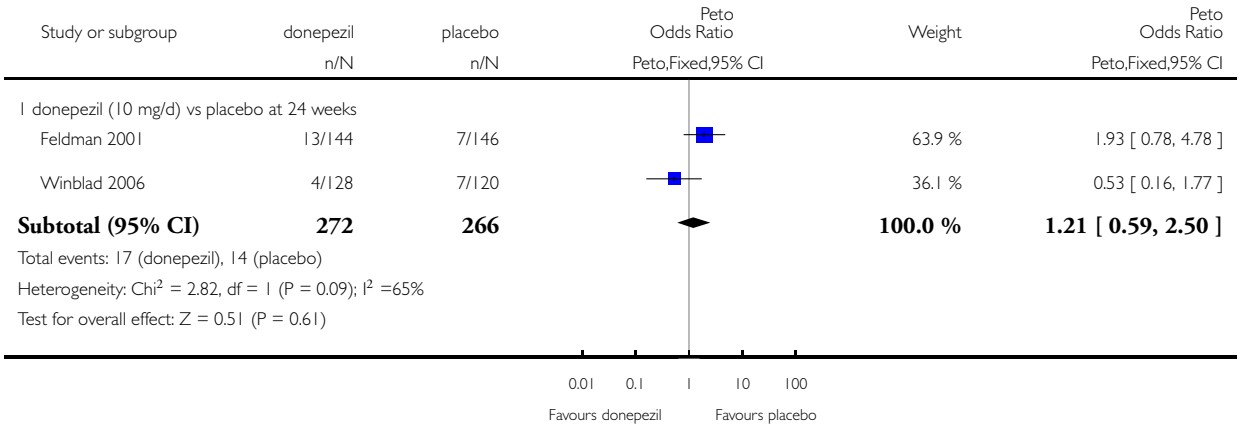


Analysis 8.17. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 17 Total number of participants who suffered from asthenia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 17 Total number of participants who suffered from asthenia

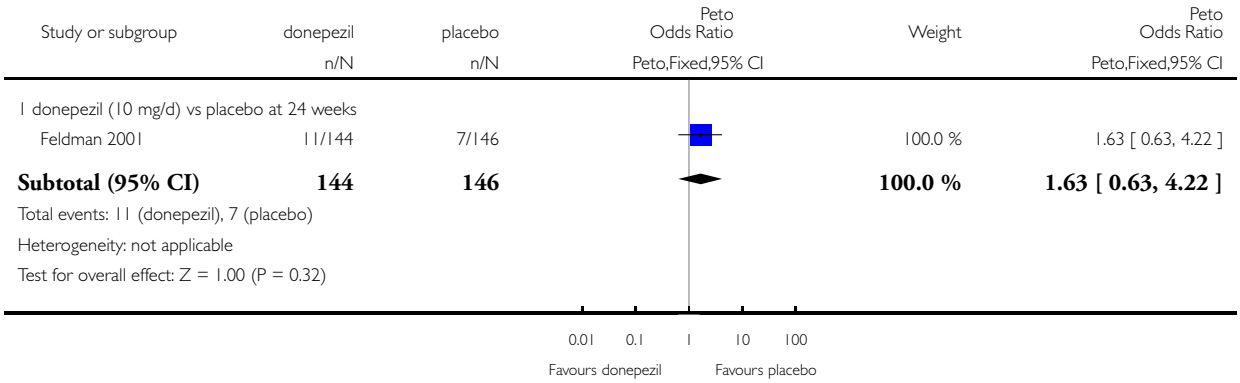


Analysis 8.18. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 18 Total number of participants who suffered from back pain.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 18 Total number of participants who suffered from back pain

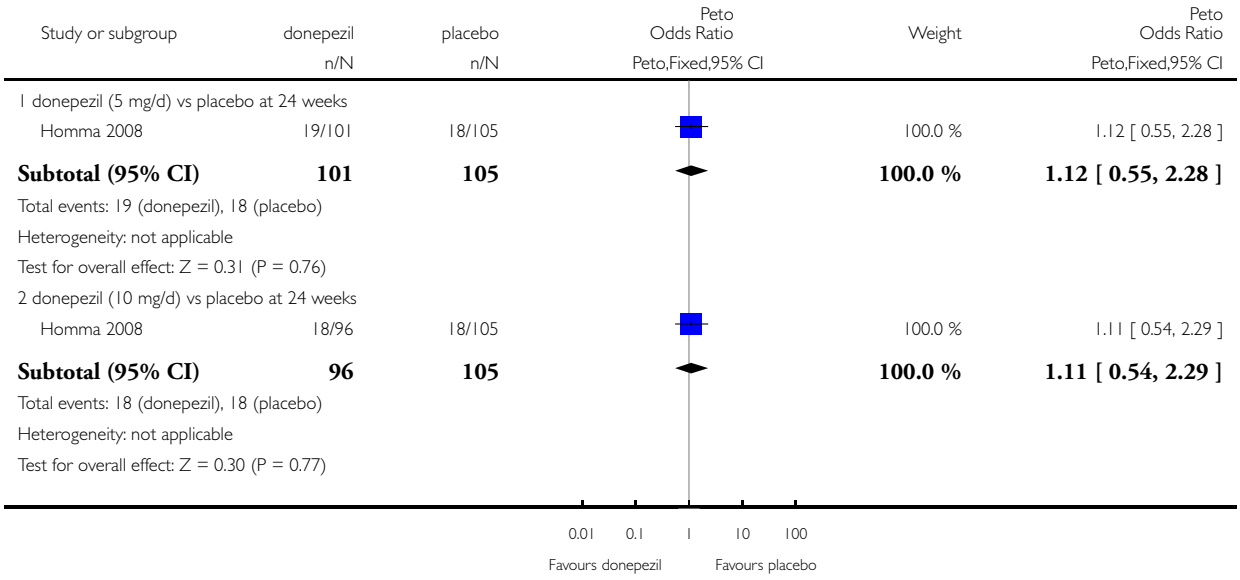


Analysis 8.19. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 19 Total number of participants who suffered from cold syndrome.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 19 Total number of participants who suffered from cold syndrome

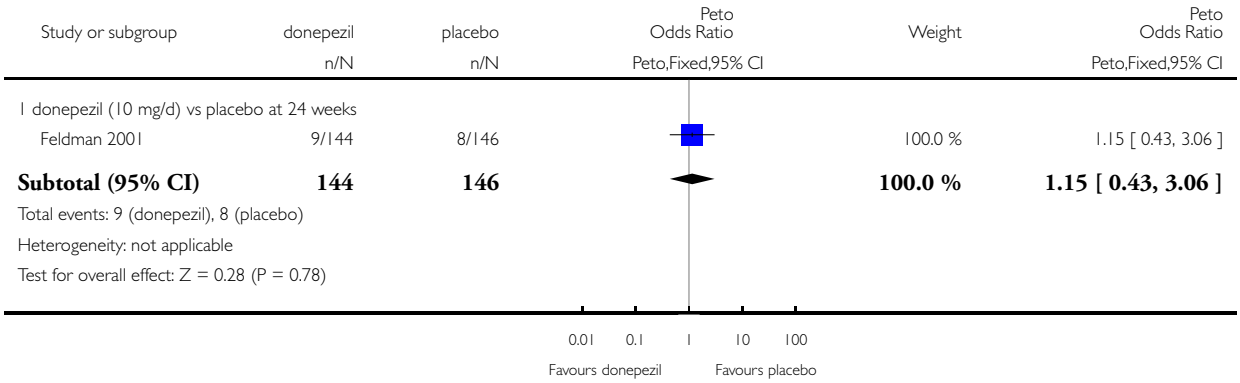


Analysis 8.20. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 20 Total number of participants who suffered from confusion.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 20 Total number of participants who suffered from confusion

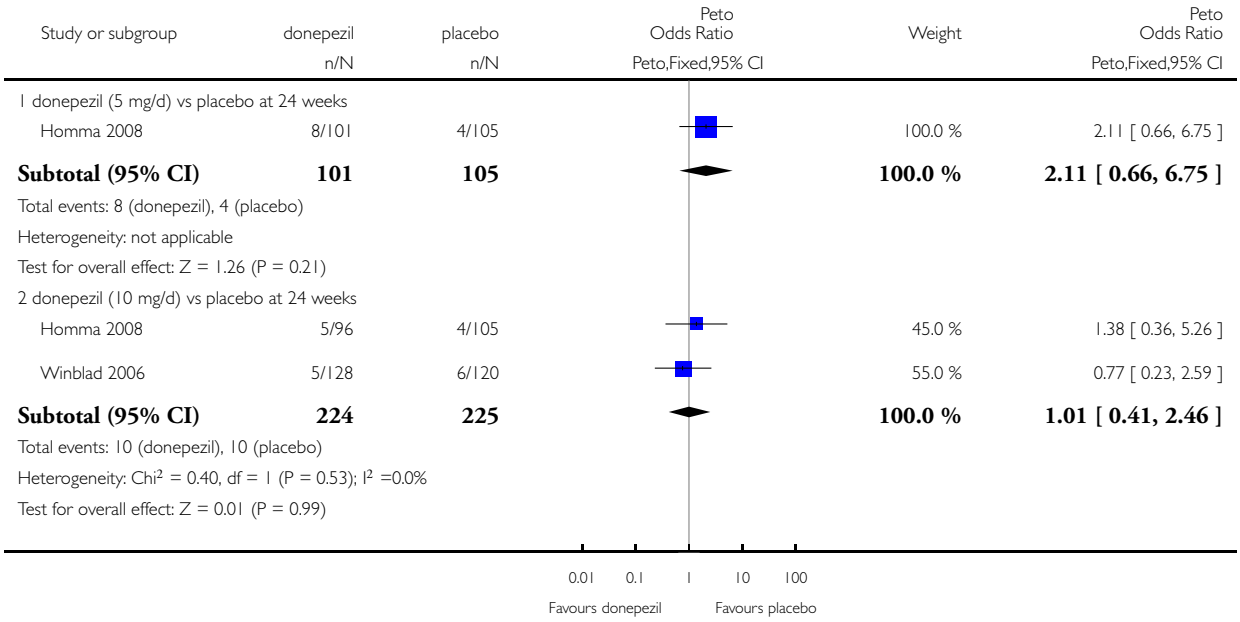


Analysis 8.21. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 21 Total number of participants who suffered from constipation.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 21 Total number of participants who suffered from constipation

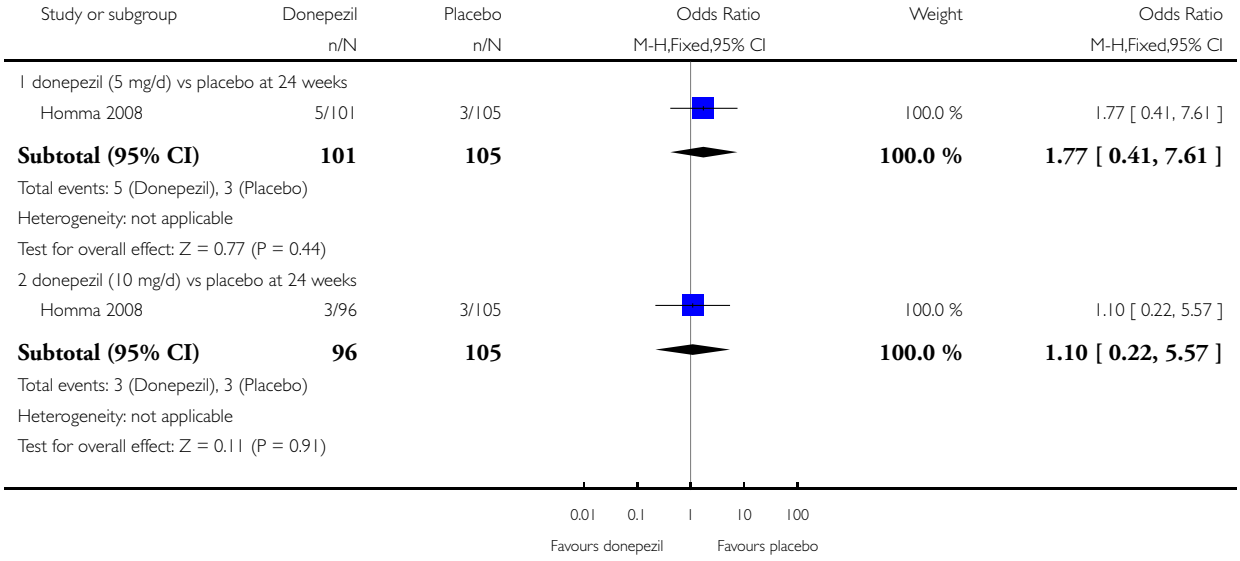


Analysis 8.22. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 22 Total number of participants who suffered from contusion.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 22 Total number of participants who suffered from contusion

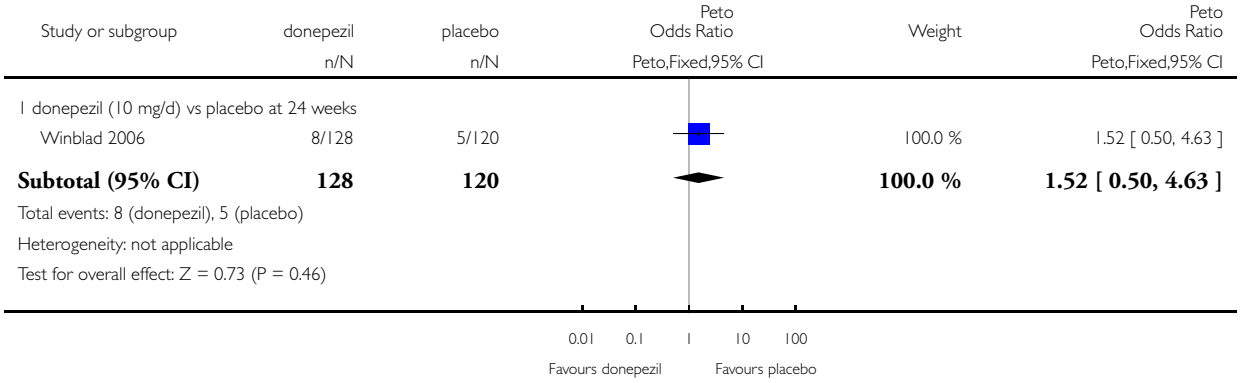


Analysis 8.23. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 23 Total number of participants who suffered from cystitis.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 23 Total number of participants who suffered from cystitis

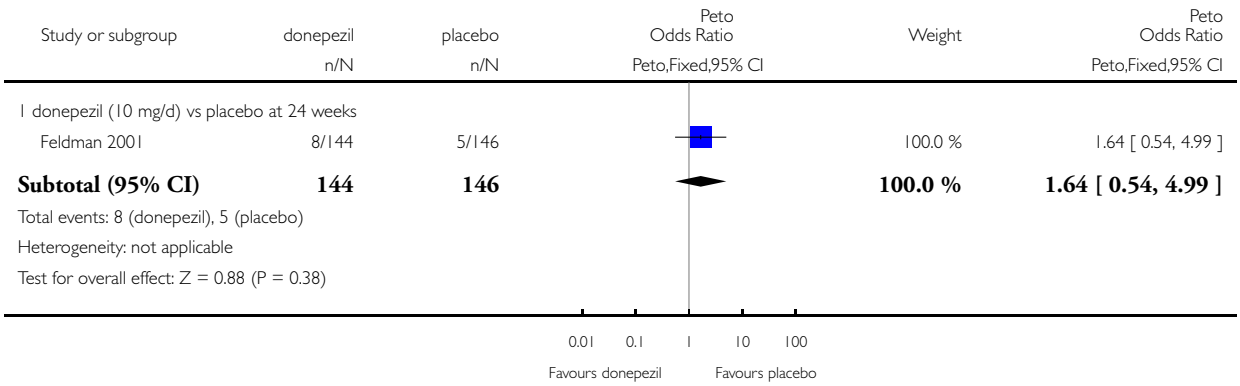


Analysis 8.24. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 24 Total number of participants who suffered from depression.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 24 Total number of participants who suffered from depression

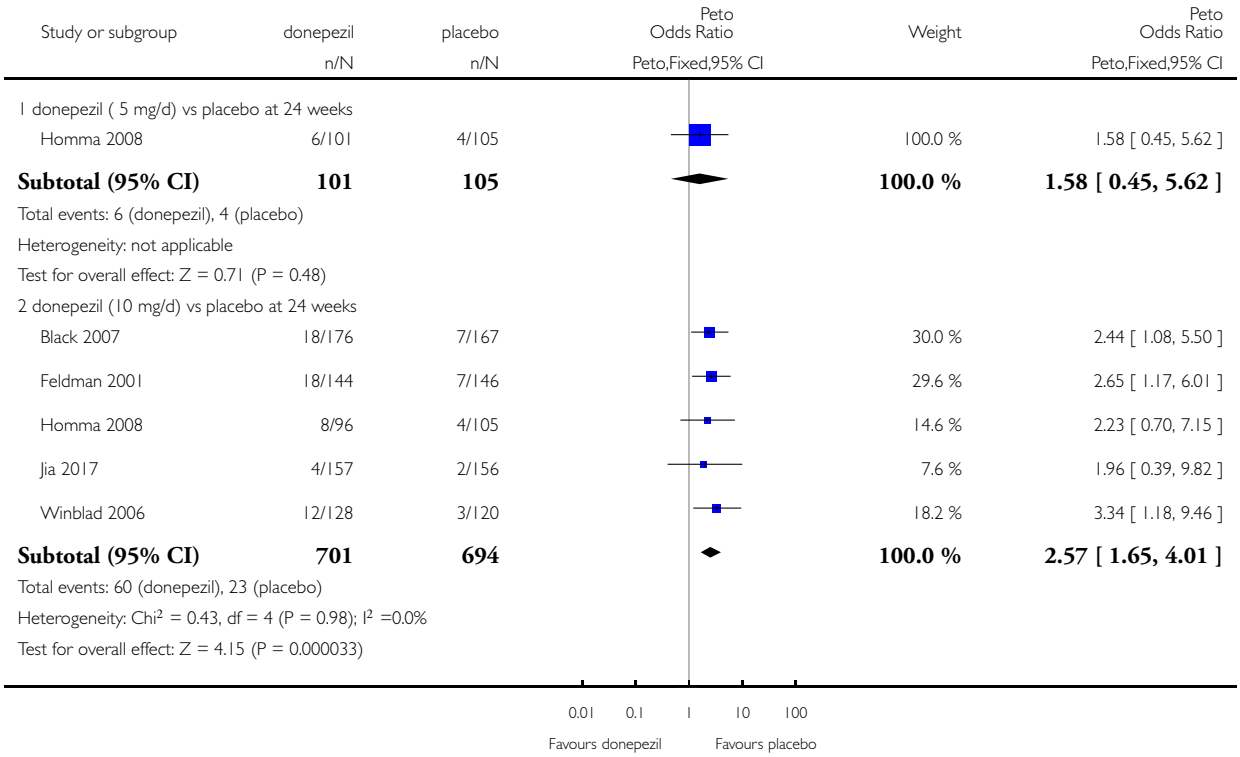


Analysis 8.25. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 25 Total number of participants who suffered from diarrhoea.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 25 Total number of participants who suffered from diarrhoea

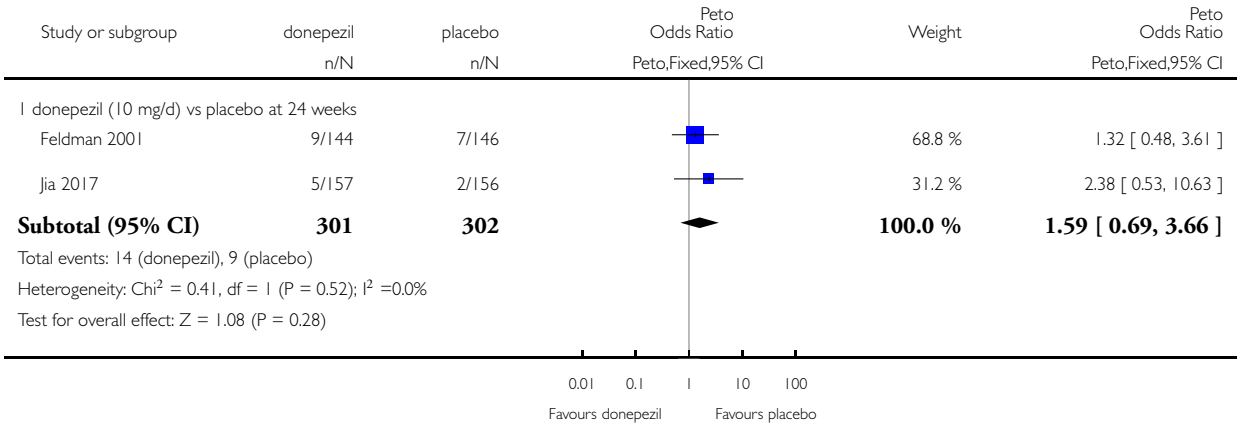


Analysis 8.26. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 26 Total number of participants who suffered from dizziness.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 26 Total number of participants who suffered from dizziness

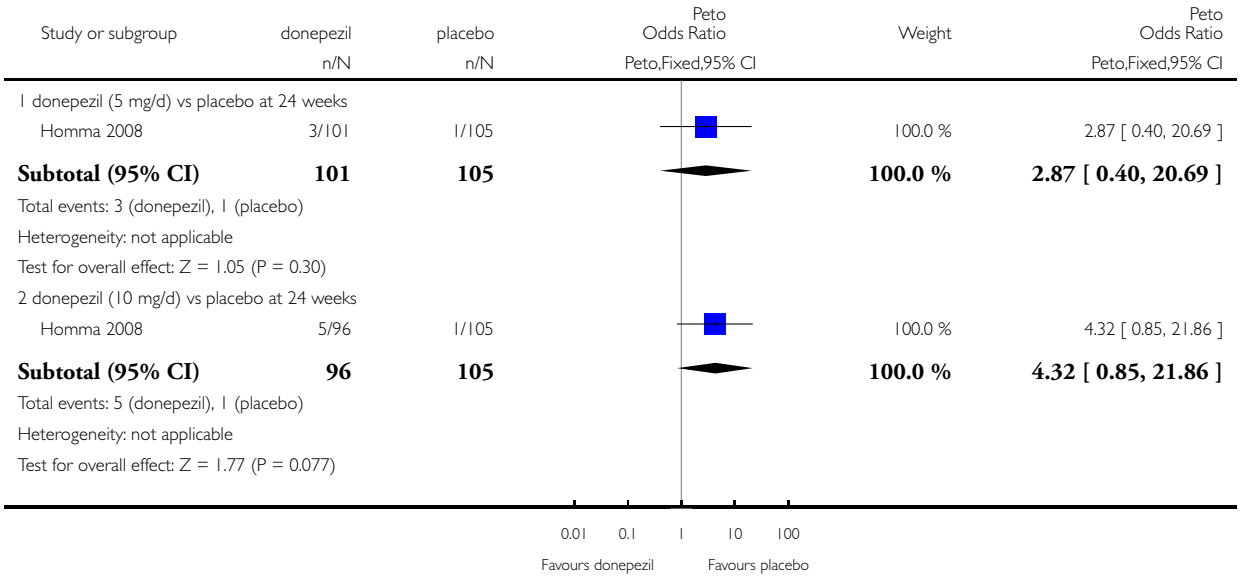


Analysis 8.27. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 27 Total number of participants who suffered from fever.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 27 Total number of participants who suffered from fever

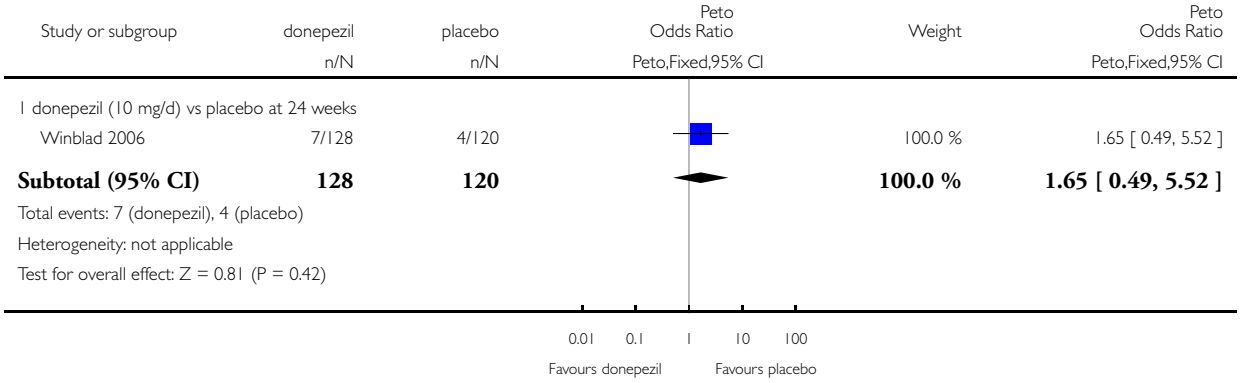


Analysis 8.28. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 28 Total number of participants who suffered from fracture.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 28 Total number of participants who suffered from fracture

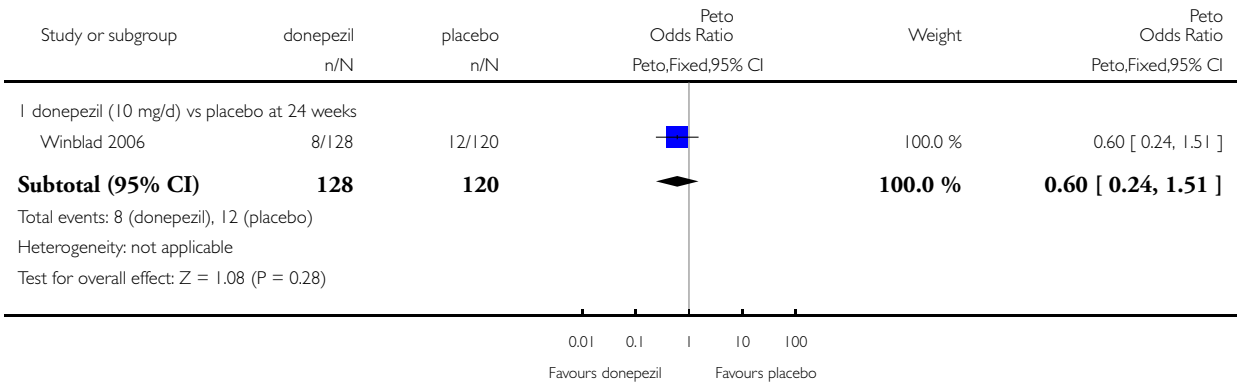


Analysis 8.29. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 29 Total number of participants who suffered from gastroenteritis.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 29 Total number of participants who suffered from gastroenteritis



Analysis 8.30. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 30 Total number of participants who suffered from hallucinations.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 30 Total number of participants who suffered from hallucinations

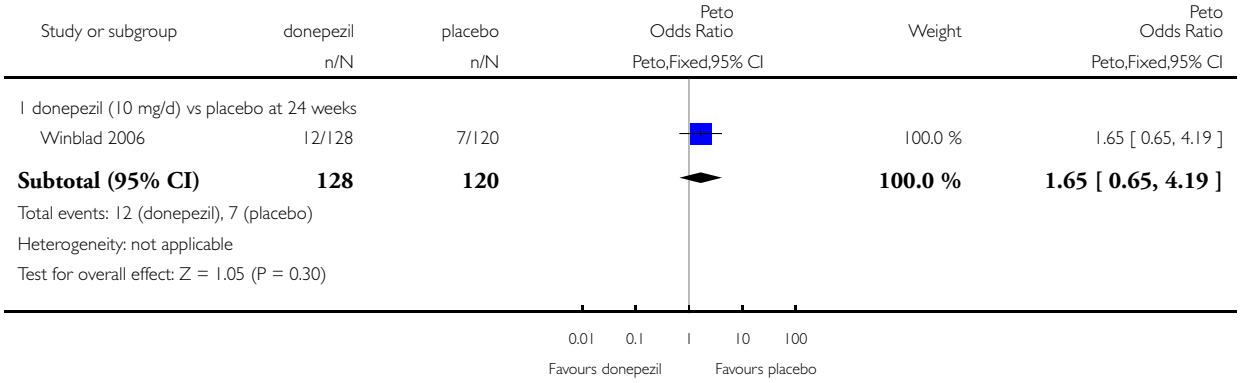
Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks					
Winblad 2006	8/128	1/120		100.0 %	4.68 [1.24, 17.66]
Subtotal (95% CI)	**128**	**120**		**100.0 %**	**4.68 [1.24, 17.66]**
Total events: 8 (donepezil), 1 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.27 (P = 0.023)					

Analysis 8.31. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 31 Total number of participants who suffered from pneumonia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 31 Total number of participants who suffered from pneumonia

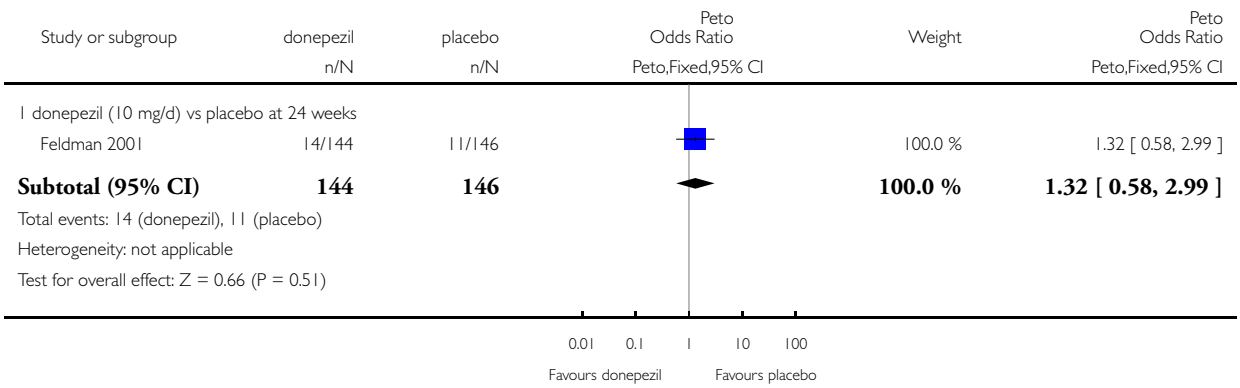


Analysis 8.32. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 32 Total number of participants who suffered from hostility.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 32 Total number of participants who suffered from hostility

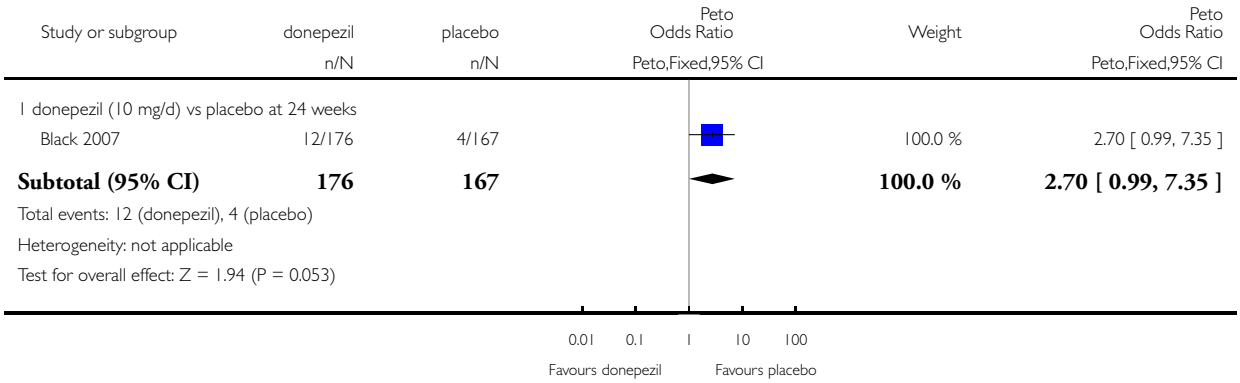


Analysis 8.33. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 33 Total number of participants who suffered from insomnia.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 33 Total number of participants who suffered from insomnia



Analysis 8.34. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 34 Total number of participants who suffered from loss of appetite.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 34 Total number of participants who suffered from loss of appetite

Study or subgroup	Donepezil n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 donepezil (5 mg/d) vs placebo at 24 weeks					
Homma 2008	5/101	2/105		100.0 %	2.68 [0.51, 14.15]
Subtotal (95% CI)	**101**	**105**		**100.0 %**	**2.68 [0.51, 14.15]**
Total events: 5 (Donepezil), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.24)					
2 donepezil (10 mg/d) vs placebo at 24 weeks					
Homma 2008	4/96	2/105		100.0 %	2.24 [0.40, 12.51]
Subtotal (95% CI)	**96**	**105**		**100.0 %**	**2.24 [0.40, 12.51]**
Total events: 4 (Donepezil), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					

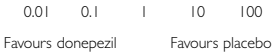
Analysis 8.35. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 35 Total number of participants who suffered from nausea.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 35 Total number of participants who suffered from nausea

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks					
Black 2007	13/176	3/167		35.9 %	3.50 [1.29, 9.54]
Feldman 2001	10/120	6/117		35.1 %	1.66 [0.60, 4.57]
Winblad 2006	8/128	5/120		29.0 %	1.52 [0.50, 4.63]
Subtotal (95% CI)	**424**	**404**		**100.0 %**	**2.11 [1.16, 3.85]**
Total events: 31 (donepezil), 14 (placebo)					
Heterogeneity: Chi^2 = 1.53, df = 2 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 2.44 (P = 0.015)					

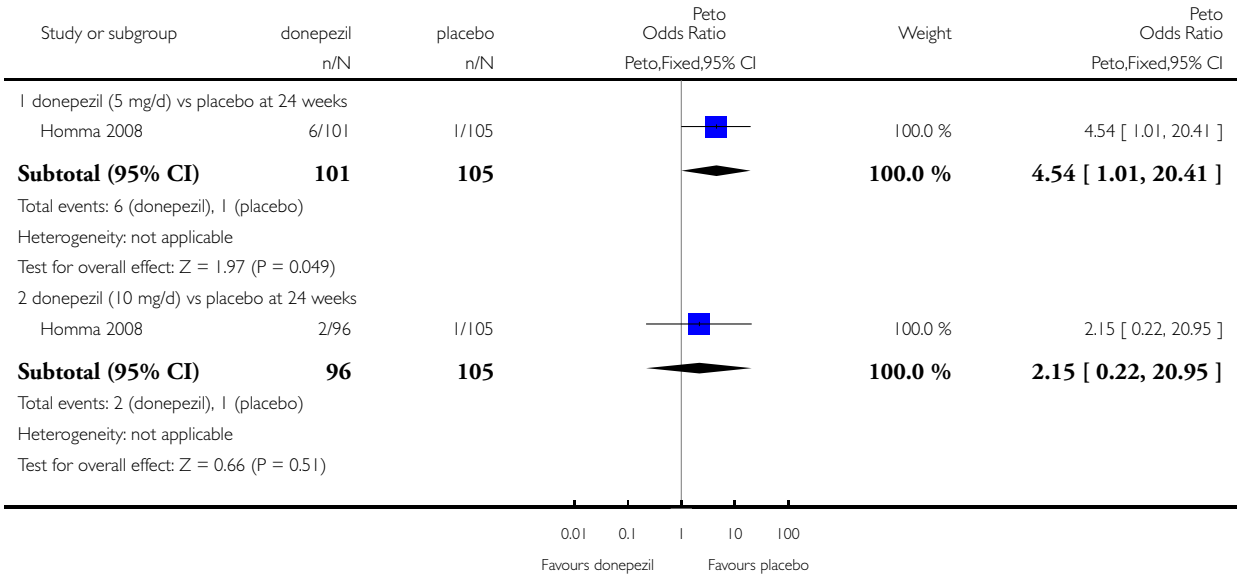


Analysis 8.36. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 36 Total number of participants who suffered from restlessness.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 36 Total number of participants who suffered from restlessness



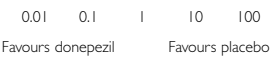
Analysis 8.37. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 37 Total number of participants who suffered from headache.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 37 Total number of participants who suffered from headache

Study or subgroup	donepezil n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 donepezil (10 mg/d) vs placebo at 24 weeks					
Feldman 2001	17/144	6/146		100.0 %	2.86 [1.22, 6.69]
Subtotal (95% CI)	**144**	**146**		**100.0 %**	**2.86 [1.22, 6.69]**
Total events: 17 (donepezil), 6 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.42 (P = 0.015)					

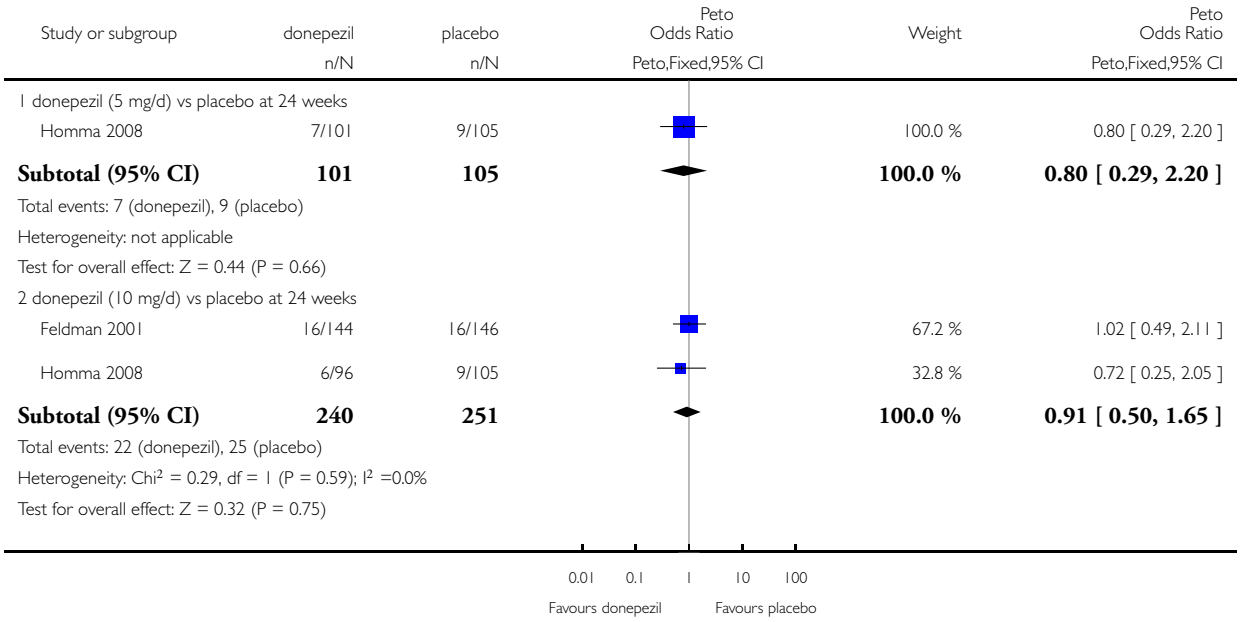


Analysis 8.38. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 38 Total number of participants who suffered from respiratory tract infection.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 38 Total number of participants who suffered from respiratory tract infection

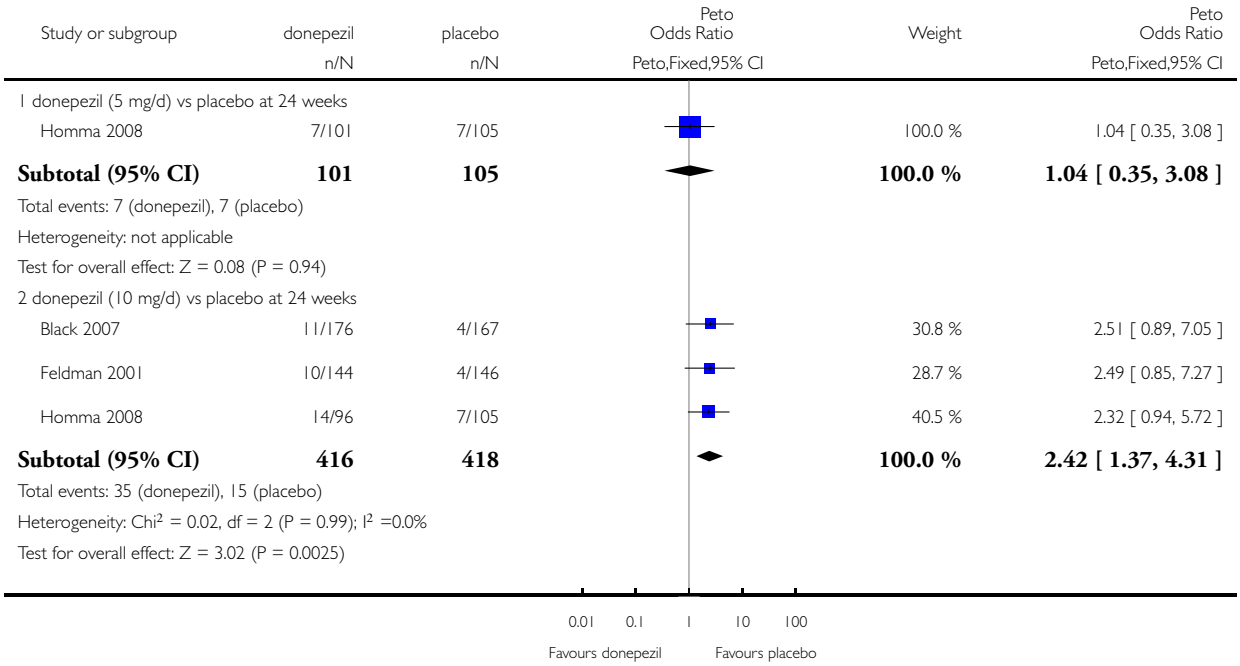


Analysis 8.39. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 39 Total number of participants who suffered from vomiting.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 39 Total number of participants who suffered from vomiting

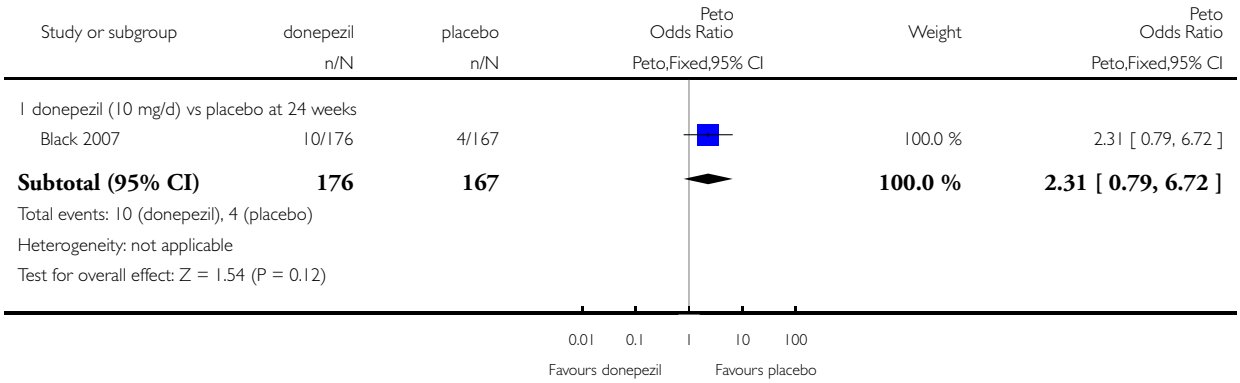


Analysis 8.40. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 40 Total number of participants who suffered from urinary incontinence.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 40 Total number of participants who suffered from urinary incontinence

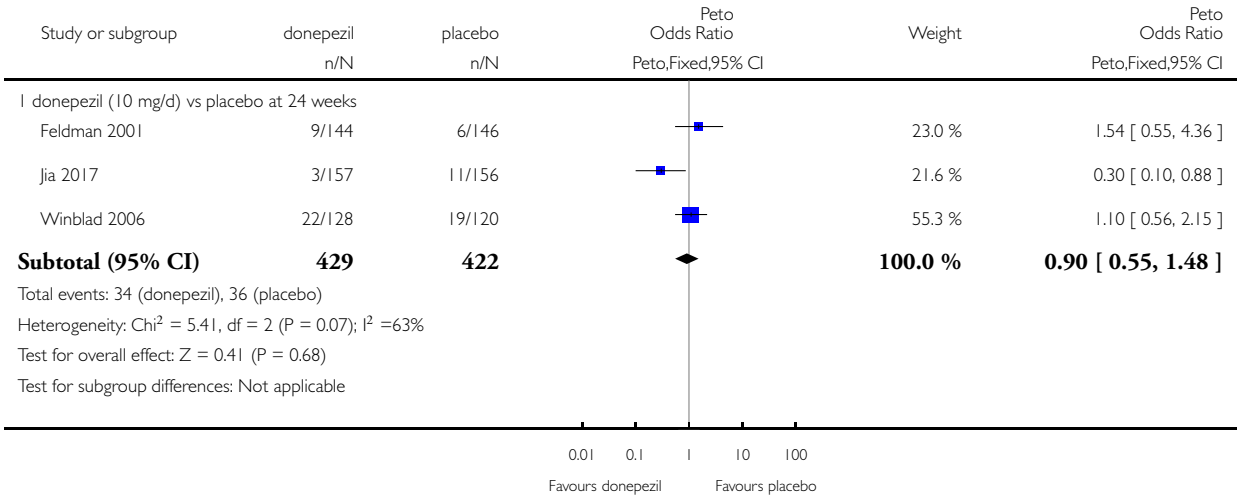


Analysis 8.41. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 41 Total number of participants who suffered from urinary tract infection.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 41 Total number of participants who suffered from urinary tract infection

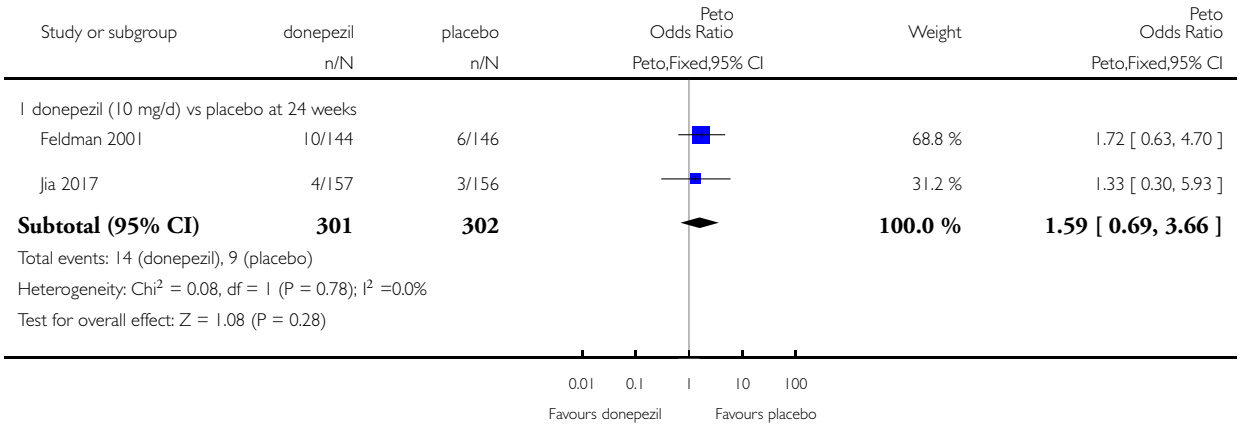


Analysis 8.42. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 42 Total number of participants who suffered from weight loss.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 42 Total number of participants who suffered from weight loss

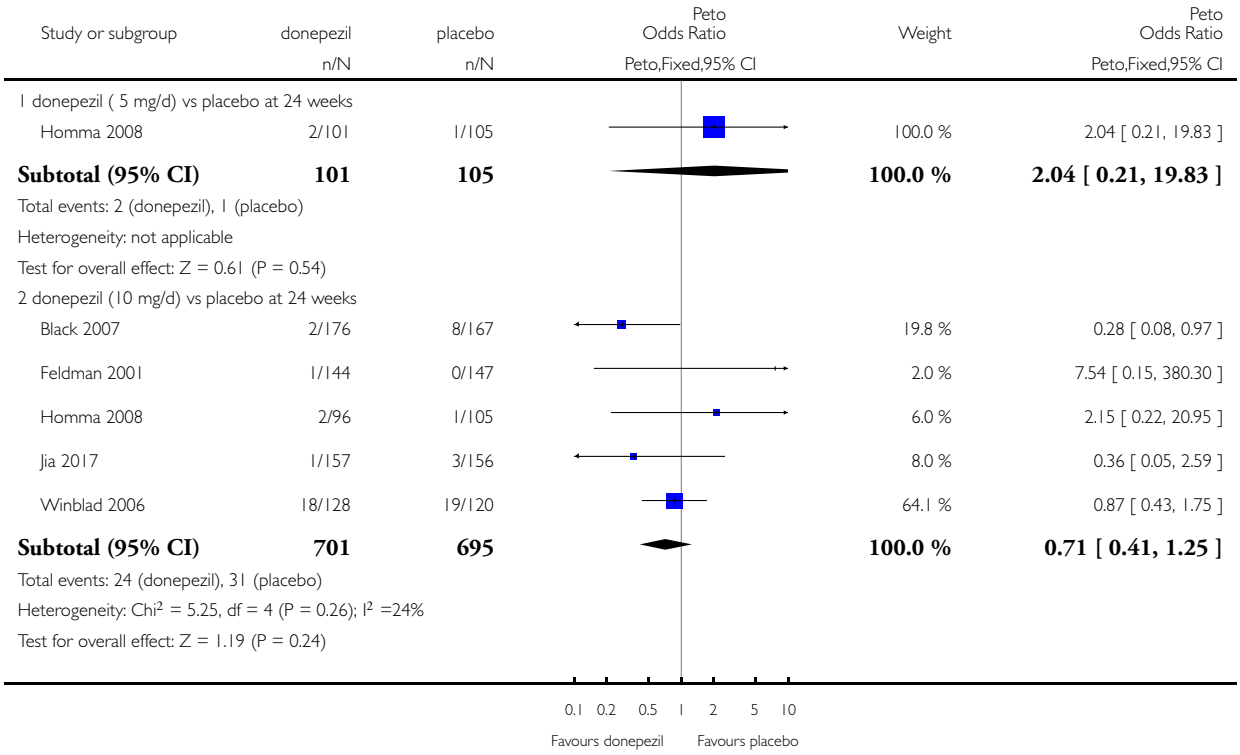


Analysis 8.43. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 43 Total number of deaths before end of treatment.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 43 Total number of deaths before end of treatment

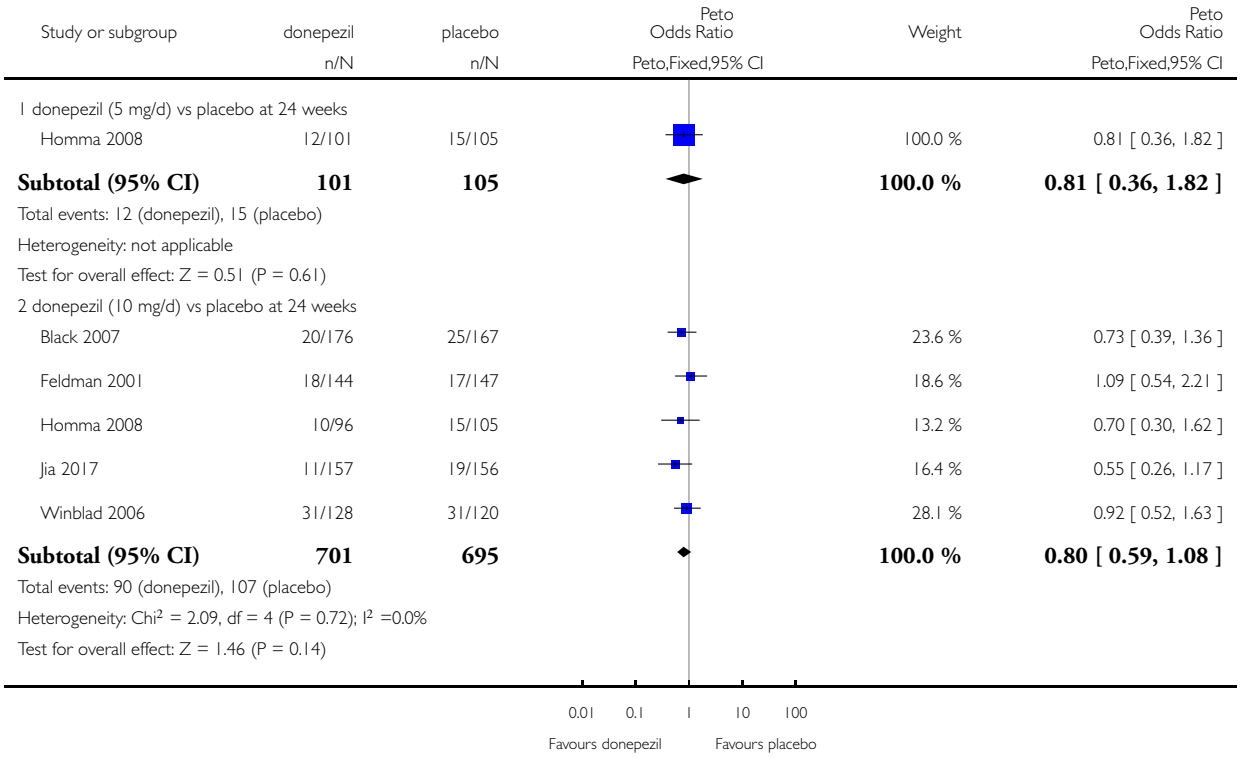


Analysis 8.44. Comparison 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia, Outcome 44 Total number of participants who suffered from at least one serious adverse event.

Review: Donepezil for dementia due to Alzheimer's disease

Comparison: 8 Donepezil (5 mg/day or 10 mg/day) versus placebo for people with severe dementia

Outcome: 44 Total number of participants who suffered from at least one serious adverse event



ADDITIONAL TABLES

Table 1. Description of included studies at baseline

Study	Duration (weeks)	Number of participants	Mean age (years)	% female	Mean MMSE	Dose mg/day donepezil	Phase	Country
Homma 1998	12	190	69.1	69	-	3, 5	II	Japan
Homma 2000	24	268	69.8	67	17.2	5	III	Japan

Table 1. Description of included studies at baseline (*Continued*)

Rogers 1996	12	161	71.8	60	18.6	1, 3, 5	II	USA
Tune 2003	24	28	73.0	75	21.0	10	-	USA
Krishnan 2003	24	67	73.4	71.6	19.2	10	-	USA
Study 205	16	12	-	-	21.4	10	-	USA
Rogers 1998a	12	468	73	63	19.5	5, 10	III	USA
Rogers 1998b	24	473	73.4	62	19.0	5, 10	III	USA
Burns 1999	24	818	71.7	57	20.0	5, 10	III	Europe
Study 306	12	39	-	-	-	10	III	Italy
Tariot 2001	24	208	85.7	82	14.4	10	III	USA
Mohs 2001	54	431	75.3	62.9	17.1	10		USA
Black 2007	24	343	78.0	68	7.5	10		Australia, Canada, France, UK, USA
Seltzer 2004	24	153	74.0	53.6	24.1	10		USA
AD2000	60	566	75.5	59	19	5, 10		UK
Lebert 1999	12	318	72.0	68	21.6	10		Unknown
Farlow 2010	24	1467	73.9			10, 23		
Feldman 2001	24	290	73.6	61.0	11.8	10		Australia, Canada, France
Hegerl 2003	12	40	-	-	-	10	III	Germany
Homma 2008	24	302	78.2	80	7.8	5, 10		Japan
Homma 2016	24	351	76.0	69.4	8.7	10, 23		Japan
Jia 2017	24	313	70.8	65	7.3	10		China
Howard 2007	12	159	84.5	85	8.2	10		England, UK

Table 1. Description of included studies at baseline (*Continued*)

Maher-Edwards 2011	24	130	71.2	67		10		Austria, Bulgaria, Chile, Estonia, Germany, The Russian Federation, Slovakia, UK
Mazza 2006	24	51	68.5	54	18.7	5		Italy
Moraes 2006a	12	23	74.7	65		10		Brazil
Moraes 2006b	26	35	76	69		10		Brazil
Winblad 2001	52	286	72.5	64	19.3	10	III	Europe
Schindler 2004	24	31	-	-	-	10,20	-	-
Winblad 2006	26	248	84.9	76.6	6.1	10	-	Sweden

MMSE: Mini-Mental State Examination

Table 2. Outcome measures

Study	MMSE	ADAS-Cog	CDR-SB	CIBIC-plus	QoL	Other
Homma 1998		X	X			MENFIS, Crichton, FGIR, GIR, OSR, GUR
Homma 2000		X	X			MENFIS, Japanese-CGIC, Crichton
Rogers 1996	X	X	X	X	X	ADL
Tune 2003		X				NPI, functional brain activity
Krishnan 2003		X				Hippocampal volumes and brain concentrations of N-acetylaspartate
Study 205	X		X		X	
Rogers 1998a	X	X	X	X	X	
Rogers 1998b	X	X	X	X	X	
Burns 1999		X	X	X	X	IDDD

Table 2. Outcome measures (*Continued*)

Study 306		X	X			
Tariot 2001	X		X			NPI-NH
Mohs 2001	X		X			ADFACS
Black 2007	X			x		SIB, ADCS-ADL-sev, NPI, CBQ, RUSP
Seltzer 2004	X	X	X			CMBT, apathy scale
AD2000						entry to institutional care, BADLS
Lebert 1999	X				X	NPI, BADLS, GHQ-30, institutionalisation
Farlow 2010	X	X		X		SIB, ADCS-ADL
Feldman 2001	X			X		SIB, CIBIS, DAD, NPI, FRS, CSS, CAUST, SF-36
Hegerl 2003		X				Hand-motor function
Homma 2008				X		SIB, ADCS-ADL-sev, BEHAVE-ADL
Homma 2016				X		SIB
Jia 2017	X			X		SIB
Howard 2007						CMAI, NPI NPI-D SIB
Maher-Edwards 2011		X		X		DAD, NPI, ACQLI
Mazza 2006	X					SKT, CGIC
Moraes 2006a		X				
Moraes 2006b		X				
Winblad 2001	X					GBS, PDS, NPI, GDS
Schindler 2004						TEAE
Winblad 2006	X					ADCS-ADL-sev, SIB, CGIC, NPI

The descriptions of the scales and tests appears in Appendix 2.

ACQLI: Alzheimer Carer's Quality of Life Instrument; **ADAS-Cog**: Alzheimer's Disease Assessment Scale;**ADCS-ADL-sev**: Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (severe version); **ADFACS**: AD Functional Assessment and Change Score; **ADL**: Activities of Daily Living; **aRSS**: abridged Relative's Stress Scale; **BADLS**: Bristol Activities of Daily Living Scale; **BEHAVE-ADL**: Behavioural Pathology in Alzheimer's Disease Activities of Daily Living; **CAUST**: Canadian Utilization of Services Tracking;

CBQ: Caregiver Burden Questionnaire; **CDR-SB**: Clinical Dementia Scale, sum of boxes; **CGIC**: Clinician's Global Impression of Change; **CIBIC+**: Clinician's Interview-Based Impression of Change;**CIBIS:** Clinician's Interview-based Impression of Severity**,** **CMAI**: Cohen-Mansfield Agitation Inventory; CSS: Caregiver Stress Scale, CMBT: Computerized Memory Battery Test, **DAD**: Disability Assessment for Dementia; FRS: Functional Rating Scale, **GBS**: Gottfries, Brane and Steen scale; **GDS**: Geriatric Depression Scale; **GHQ-30**: General Health Questionnaire; **IDDD**: Interview for Deterioration in Daily living in Dementia scale; **MENFIS**: Mental Function Impairment Scale; **MMSE**: Mini Mental State Examination; **NOSGER**: Nurses' Observation Scale for Geriatric Patients; **NPI**: Neuropsychiatric Instrument; **NPI-D**: Neuropsychiatric Inventory Distress scale; **NPI-NH**: Neuropsychiatric Inventory Nursing Home version **PDS**: Progressive Deterioration Scale; **QoL**: Quality of Life; **RUSP**: Resources Utilisation for Severe Alzheimer's Disease Patients; **SF-36**: Short Form - 36; **SKT**: Syndrom Kurz Test; **SIB**: Severe Impairment Battery; **TEAE**: treatment-emergent adverse event

Table 3. Study objectives

Study	Objectives
AD2000	"We aimed to determine whether donepezil produces worthwhile improvements in disability, dependency, behavioural and psychological symptoms, carers' psychological wellbeing, or delay in institutionalisation. If so, which patients benefit, from what dose, and for how long?"
Black 2007	"To evaluate the safety and efficacy of donepezil for severe Alzheimer disease (AD)."
Burns 1999	"To evaluate the efficacy and safety of once-daily administration of donepezil at doses of 5 and 10 mg versus placebo in a large, multinational cohort of patients with mild-moderately severe Alzheimer's disease"
Farlow 2010	"The objective of this study was to compare the effectiveness and safety profile of high-dose donepezil (23 mg/day) and standard dose donepezil (10 mg/day) in patients with moderate to severe AD"
Feldman 2001	"To investigate the efficacy and safety of donepezil in patients with moderate to severe AD"
Hegerl 2003	"To evaluate the effects of donepezil on hand motor function in patients with mild-moderate AD"
Homma 1998	"To evaluate efficacy, safety and the optimal dose of E2020 in patients with mild to moderate Alzheimer-type dementia"
Homma 2000	"To evaluate the efficacy and safety of donepezil hydrochloride (donepezil) at 5mg/day in patients with mild to moderately Alzheimer's disease for 24 weeks"
Homma 2008	"A 24-week, randomized, parallel-group, double-blind placebo-controlled study was conducted to evaluate the efficacy and tolerability of donepezil in severe Alzheimer's disease (AD)."
Homma 2016	"To demonstrate the superiority of SR 23 mg/day donepezil over IR 10 mg/day donepezil in Japanese patients with severe AD (SAD)."
Howard 2007	"The primary question was whether donepezil is better than placebo in the management of agitation that is inappropriate for, or has not responded to, a psychosocial treatment."

Table 3. Study objectives (*Continued*)

Jia 2017	"To examine the effects of donepezil on N-acetylaspartate concentration and hippocampal volume in patients with mild-moderate AD"
Krishnan 2003	"The authors examined the effect of the acetylcholinesterase inhibitor donepezil on magnetic resonance markers of neurodegeneration in Alzheimer's disease."
Lebert 1999	AD2000 is a large, simple, 'real-life' trial that aims to produce reliable evidence on the value of donepezil (Aricept®) in routine practice
Maher-Edwards 2011	"This exploratory study was designed to estimate the effects of donepezil and SB-742457 in a current day setting and population using a study design similar to those employed in two pivotal studies with donepezil (Rogers 1998b, Burns 1999)"
Mazza 2006	"To assess the efficacy of Ginkgo biloba special extract in patients with dementia of the Alzheimer type in slowing down the disease's progression and patient's cognitive impairment compared with donepezil and placebo"
Mohs 2001	"To examine the effects of donepezil compared with placebo on the preservation of function in patients with AD over a 1-year period"
Moraes 2006a	"This study evaluates the effects of donepezil on obstructive sleep apnea in patients with Alzheimer disease."
Moraes 2006b	"Examine the effects of donepezil on sleep and rapid eye movement (REM) sleep electroencephalogram (EEG) in patients with Alzheimer disease, using polysomnography"
Rogers 1996	"To evaluate the efficacy and safety of donepezil in patients with mild to moderately severe Alzheimer's disease and to examine the relationships between plasma donepezil concentration, red blood cell acetylcholinesterase activity and clinical response"
Rogers 1998a	"The present phase I11 study was undertaken to further evaluate the efficacy and safety of donepezil at dosage levels of 5 and 10 mg/d versus placebo in patients with mild to moderate AD"
Rogers 1998b	"This phase 3 study was 1 of 2 pivotal trials undertaken to establish the efficacy and safety of using donepezil in patients with mild to moderately severe Alzheimer disease"
Schindler 2004	"To determine the safety and tolerability of treatment with 15 or 20 mg/day donepezil in mild to moderate AD"
Seltzer 2004	"To evaluate the efficacy of donepezil in patients with early-stage Alzheimer disease"
Study 205	"To evaluate the effect of donepezil on visuospatial attention in Alzheimer's disease patients"
Study 306	"To evaluate the utility of APo-E subtype in predicting response to treatment with donepezil in Alzheimer's disease patients"

Table 3. Study objectives (*Continued*)

Tariot 2001	"To evaluate the safety and efficacy of donepezil in the management of patients with Alzheimer's disease (AD) residing in nursing home facilities."
Tune 2003	"This study evaluated the effects of donepezil on functional brain activity in patients with AD."
Winblad 2001	"To evaluate the long-term clinical efficacy and safety of donepezil versus placebo over 1 year in patients with mild to moderate AD."
Winblad 2006	"Our aim was to assess the eff ect of donepezil on cognition and activities of daily living in patients with severe Alzheimer's disease living in nursing homes ran by trained staff ."

AD: Alzheimer's disease; **SAD**: severe Alzheimer's disease;; **REM:** rapid eye movement

APPENDICES

Appendix 1. Sources searched and search strategies used (Jan 2015, Nov 2015, Nov 2016, May 2017))

Source	Search strategy	Hits
Medline (Ovid SP) [Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to May 19, 2017] [Date of most recent search: 20 May 2017]	1. donepezil.mp. 2. aricept*.mp. 3. donezepil.ti,ab. 4. E2020 5. or/1-4 6. dement*.ti,ab. 7. alzheimer*.ti,ab. 8. exp Dementia/ 9. or/6-8 10. randomized controlled trial.pt. 11. controlled clinical trial.pt. 12. randomized.ab. 13. placebo.ab. 14. drug therapy.fs. 15. randomly.ab. 16. trial.ab. 17. groups.ab. 18. or/10-17 19. 5 and 9 and 18	Jan 2015: 2010 Nov 2015: 192 Nov 2016: 148 May 2017: 166

(*Continued*)

Embase (Ovid SP) [1974 to 2017 May 19] [Date of most recent search: 20 May 2017]	1. donepezil.mp. 2. aricept*.mp. 3. donezepil.ti,ab. 4. E2020 5. or/1-4 6. dement*.ti,ab. 7. alzheimer*.ti,ab. 8. exp Dementia/ 9. or/6-8 10. randomized controlled trial.pt. 11. controlled clinical trial.pt. 12. randomized.ab. 13. placebo.ab. 14. drug therapy.fs. 15. randomly.ab. 16. trial.ab. 17. groups.ab. 18. or/10-17 19. 5 and 9 and 18	Jan 2015: 1065 Nov 2015: 263 Nov 2016: 91 May 2017: 184
Cinahl (EBSCOhost) [Date of most recent search: 20 May 2017]	S1 (MM "Donepezil") S2 TX donepezil S3 TX donezepil S4 TX aricept S5 S1 or S2 or S3 or S4 S6 (MH "Dementia+") S7 TX dement* S8 TX alzheimer* S9 S6 or S7 or S8 S10 TX random* S11 (MH "Clinical Trials+") S12 TX placebo S13 TX trial S14 TX "control group" S15 S10 or S11 or S12 or S13 or S14 S16 S5 and S9 and S15	Jan 2015: 64 Nov 2015: 15 Nov 2016: 6 May 2017: 6
PsycINFO (Ovid SP) [1806 to May Week 2 2017] [Date of most recent search: 20 May 2017]	1. donepezil.mp. 2. aricept*.mp. 3. donezepil.ti,ab. 4. E2020 5. or/1-4 6. dement*.ti,ab. 7. alzheimer*.ti,ab. 8. exp dementia/ 9. or/6-8 10. exp Clinical Trials/ 11. random*.ti,ab. 12. randomized.ab.	Jan 2015: 375 Nov 2015: 48 Nov 2016: 0 May 2017: 7

(*Continued*)

	13. placebo.ab. 14. trial.ab. 15. groups.ab. 16. or/10-15 17. 5 and 9 and 16	
LILACs (BIREME) [Date of most recent search: 20 May 2017]	(E2020 OR donepezil OR Aricept) AND (Alzheimer$ OR dementia OR ((cognit$ or memory$ or mental$) and (declin$ or impair$ or los$ or deteriorat$)) AND (randomized OR randomized OR double blind$ OR single blind$ OR placebo$ OR controlled)	Jan 2015: 2 Nov 2015: 9 Nov 2016: 0 May 2017: 0
ALOIS (CRS Web) [Date of most recent search: 20 May 2017]	(E2020 OR donepezil OR Aricept)	Jan 2015: 6 Nov 2015: 16 Nov 2016: 2 May 2017: 0
CENTRAL, The Cochrane Library, Issue 5 [Date of most recent search: 20 May 2017]	(E2020 OR donepezil OR Aricept) AND (Alzheimer* OR dementia OR ((cognit* or memory* or mental*) and (declin* or impair* or los* or deteriorat*))	Jan 2015: 138 Nov 2015: 20 Nov 2016: 66 May 2017: 110
Web of Science Core Collection [ISI Web of Science] [Date of most recent search: 20 May 2017]	**TOPIC:** (donepezil OR aricept*) *AND* **TOPIC:** (dementia OR alzheimer* OR "cognit* impair*") *AND* **TOPIC:** (random* OR trial OR placebo OR "double blind*" OR "blinded" OR "single blind*" OR "control group*")	Nov 2015:252 Nov 2016: 201 May 2017: 141
ICTRP (WHO portal) [Date of most recent search: 20 May 2017]	(E2020 OR donepezil OR Aricept) AND (Alzheimer* OR dementia)	Nov 2015: 18 Nov 2016: 2 May 2017: 0
ClinicalTrials.gov [Date of most recent search: 20 May 2017]	(E2020 OR donepezil OR Aricept) AND Alzheimer* OR dmentia)	Jan 2015: 21 Nov 2015: 5 Nov 2016: 2 May 2017: 0
Total before de-duplication		Jan 2015: 3681 Nov 2015: 840 Nov 2016: 518 May 2017: 614 TOTAL: 5653
Total after de-duplication		Jan 2015: 3201 Nov 2015: 618 Nov 2016: 411

(*Continued*)

	May 2017: 423 TOTAL:
Total after first assessment by CDCIG information specialist	Jan 2015: 44 Nov 2015: 41 Nov 2016: 14 May 2017: 6 TOTAL: 106

Appendix 2. Description of tests and rating scales

Cognitive Function

- The primary cognitive test in nine studies was the cognitive part of the **Alzheimer's Disease Assessment Scale (ADAS-Cog)** (Rosen 1984), modified and called the ADAS-Jcog for Japanese patients. ADAS-Cog comprises 11 individual tests, spoken language ability (0-5), comprehension of spoken language (0-5), recall of test instructions (0-5), word finding difficulty (0-5), following commands (0-5), naming object (0-5), construction drawing (0-5), ideational praxis (0-5), orientation (0-8), word recall (0-10) and word recognition (0-12). The total score ranges from 0-70, the high score indicating greater impairment. The ADAS-Jcog is not quite equivalent to the ADAS-Cog, using ideograms and ideographic memory as well as verbal memory. The scoring and subtests are different.
- **Mini Mental State Examination (MMSE)** (Folstein 1975) evaluates cognition in five areas: orientation, immediate recall, attention and calculation, delayed recall, and language. The test takes only 15 minutes to administer and the score ranges from 0 (severe impairment) to 30 (normal).
- The **Quality of Life (QoL)** (Blau 1977) is a self-rated, seven-item scale, based on a 'social indicators' approach, examining relationships, eating and sleeping, and social and leisure activity. The items are scored on an analogue scale between 0 (worst quality) and 50 (best). The Blau scale originally contained 10 items, and it is unclear both how the seven items were chosen, and whether the scale has been validated for use in people with dementia.
- The **Severe Impairment Battery (SIB)** (Panisset 1994) is a 40-item questionnaire designed to assess the severity of cognitive dysfunction in advanced AD and is divided into nine domains: memory, language, orientation, attention, praxis, visuospatial, construction, orientation to name, and social interaction. The score ranges from 0 (greatest impairment) to 100 (no impairment).
- The **Syndrom Kurz Test (SKT)** (Overall 1992) is a brief psychometric test battery for the assessment of memory and attention. There are nine subtests, six speed orientated (language fluency, number fluency, attention planning and praxis, short-term memory, attention and concentration) and three span orientated (short-term visual memory, long-term memory span and recognition memory span) resulting in a score 0 to 27(severe impairment).

Activities of daily living (ADLs)

- The Winblad 2001 used the **Progressive Deterioration Scale (PDS)** (DeJong 1989), which is a disease-specific measure of changes in 29 items of the ADLs. The interview is conducted with the caregiver. DeJong describes this scale as a measure of quality of life for Alzheimer's disease, on account of the correlation between ability to perform ADLs and quality of life.
- Homma 2000 used the **CMCS**, which is derived from the **Crichton geriatric rating scale**. A nine-point scoring system, from 0 (normal function) to 8 (maximum disturbance or presence of symptoms) measures orientation, communication, co-operation, restlessness, ability to dress, work and social activities and leisure. The range of scores is 0 to 56. Strictly this scale is a more comprehensive scale than an ADL scale.
- Feldman 2001 used the **Disability Assessment for Dementia (DAD)** (Gélinas 1999) a 10-domain, 40-item instrument that measures instrumental and basic ADLs. A higher score indicates less behavioural symptomatology.
- Feldman 2001 used the **Instrumental Activities of Daily Living (IADL)** (Lawton 1969), modified to assess people with moderate to severe dementia. The IADL scale assesses the ability to perform eight complex daily tasks: ability to use the telephone, shopping, food preparation, household tasks, laundry, transportation, responsibility for medications and ability to manage finances.

The modified version omits the laundry item and includes items from the **Alzheimer's Disease Functional Assessment Change Scale (ADFACS)** relating to managing household appliances, mail, hobbies and the ability to get around inland outside home.

- Feldman 2001 uses the **Physical Self Maintenance Scale (PSMS)** (Lawton 1969), a six-item scale that rates self-care ability (toileting, feeding, dressing, personal hygiene, locomotion and bathing). The modified version used includes three extra items believed to be important for the provision of basic ADL in moderate to severe Alzheimer's disease (loss of recognition of carer, impaired ambulation and wandering).
- AD2000 used the **Bristol Activities of Daily Living Scale (BADLS)** (Bucks 1996).
- Winblad 2006 used the **Modified Alzheimer's Disease Cooperative Study activities of daily living inventory for severe Alzheimer's disease (ADCS-ADL-severe)** (Galasko 2000). This is a 19-item scale for basic and complex abilities validated in people with moderate to severe dementia. Total score ranges from 0 to 54 (no impairment). Items include basic ADLs (eating, bathing and complex (operating taps, switching lights).

Global Assessment

- A **Clinician's Interview-Based Impression of Change scale (CIBIC-Plus)** (Schneider 1997) was used in four studies. It provides a global rating of patient function in four areas, general, cognitive, behaviour and ADLs. All patients are scored on global severity at baseline and subsequent assessments on a scale of 1 to 7 are relative to baseline, with 1 showing marked improvement, 7 marked worsening with 4 representing no change. Information is obtained from the caregiver and patient and the clinician is blind to all other measures.
- The Winblad 2001 used the **Gottfries, Brane and Steen scale (GBS)** (Gottfries 1982) for the global assessment. The GBS is a comprehensive scale for rating dementia syndromes, based on a semi-structured interview with the caregiver. A seven-point scoring system, from 0 (normal function) to 6 (maximum disturbance or presence of symptoms) measures orientation, memory and concentration (12 items), ADLs (6 items), emotional function (3 items) and pathological aspects of behaviour (6 items).
- **Clinical Rating Scale (CDR)** (Berg 1988) is usually reported as a score, 0.5, 1, 2, 3 but these scores are derived from ratings in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care), each scored from 0 (normal) to 3 (severe dementia) and the sum of the ratings (0 to 18) provides the **CDR-sum of boxes (CDR-SB)**.
- Homma 2000 used the **Mental Function Impairment Scale (MENFIS)** (Homma 1991) which is a modification of the GBS. It evaluates cognitive function (7 items), motivational function (3 items) and emotional function (3 items).
- Winblad 2006 used the **Cinical Global Impression of Improvement scale (CGI-C)** (ECDEU 1976).

Behavioural Disturbance

- The **Neuropsychiatric Instrument (NPI)** (Cummings 1994), a 12-item, carer-rated instrument, was used by Feldman 2001, and Tariot 2001 to evaluate behavioural and neuropsychiatric symptoms, including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time behaviour, and appetite/eating disorder. Frequency is rated from 1 (occasional, less than once a week) to 4 (very frequent) and severity from 1 (mild) to 3 (severe). The product of frequency and severity ranges from 1 to 12, with a total score ranging from 12 to 120 for the 10 domains summed. A lower score indicates improvement.
- The **Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)** (Reisberg 1987) a secondary outcome in the Homma 2008 study, assesses paranoid and delusional ideations, hallucinations, activity disturbance, aggressiveness, diurnal rhythm disturbances, affective disturbances and anxieties and phobias; each item is scored from 0 (none) to 3 (most severe). Scores range from 0 to 78, with higher scores indicating more severe symptoms.
- **Cohen-Mansfield Agitation Inventory (CMAI)** (Cohen-Mansfield 1987) (on a scale of 29 to 203, with higher scores indicating more agitation) was used in the Howard 2007 trial.

Stress on carers

- The abridged **Relative Stress Scale (aRSS)** is a self-assessment scale for carers. They rate their stress on a scale of 0 (not at all) to 4 (extreme stress) on 10 items that cover their experience of dealing with a person with Alzheimer's disease. This outcome was assessed only in the Lebert 1999 trial.
- The **Neuropsychiatric Inventory Distress scale (NPI-D)** assesses the degree of distress caused to the carer by the 10 individual items (each scores 0 to 5) of the NPI.

- AD2000 assessed the psychological well-being of the carer using the **General Health Questionnaire (GHQ-30)** (0-30) (Goldberg 1988).
- Black 2007 assessed the time and stress associated with assisting the patient with performance of daily tasks using the **Caregiver Burden Questionnaire (CBQ)**.

Health resource utilisation

- This outcome is assessed in the Feldman 2001 study.
    - At a time within two days of a clinic visit, carers kept records of the time per day they spent assisting with instrumental and basic ADL using a version of the IADL+ and the PSMS scale. The total time over the study period was calculated by multiplying the estimate per day by the number of days since the last clinic visit. The utilisation of health resources by patients and carers was measured using the **Canadian Utilization of Services Tracking (CAUST)** questionnaire and the carer time assessment. This covered many items that belonged to one of the following categories: community medical care, hospitalisations and residential care for the patient and medical care, hospitalisations and counselling for the carer.
    - The analysis of the CAUST data included those services that were considered to be AD-related.
    - For those who left the study before the end, the use of services over the entire 24-week period was estimated using the LOCF principle. For other missing data, where there was no previous observation, imputed values were used based on the assessment data of patients from the same country of similar MMSE.
    - Costs were calculated for patients and carers in each treatment group based on unit prices, based on Ontario fees schedules regardless of the country in which the patient lived for each resource. There are estimates of costs for carer time helping with ADLs, based on the average Ontario minimum wage of CAD 6.85/hour.
    - Although the health resource utilisation was quite different over the three countries, Australia, Canada and France, the mean for each item over all participants was used in the analyses. The group means and mean costs for each item, summaries over categories and overall totals were reported. The costs were assessed in 1998.
- Winblad 2001 also reported on the direct and indirect costs of caring for a person with Alzheimer's disease, and included the informal costs for care provided by the carer, assessed using the **Resource Utilization in Dementia (RUD)** (Wimo 1998) questionnaire at baseline, and weeks 12, 24, 36 and 52. RUD covers the patients' study medication, use of social services and living accommodation; patients' and carers' hospitalisation, visits to healthcare professionals, concomitant medication; and carers' time caring for patients or missed work. The study included people from Finland and Sweden, with smaller numbers from Norway, Denmark and the Netherlands. The costs were reported in 1999 values, converted from Swedish Kroner to USD, using a mean conversion rate for 1999.
- Black 2007 assessed the resources used by the participant, accomodation, visits to emergency department, hospitalizations, visiting nurse, home health aid, day care, respite care, meal delivery using the **Resources used by Patient (RUSP)** scale.

FEEDBACK

Review does not answer carer's questions

Summary

A carer found this review did not answer many of her questions.
"As carer for someone with Alzheimers who is taking Aricept, this review did not answer many of my questions. For example, the description of participants uses language I do not understand. What do all the initials mean (ICD-10, DSM and NINCDS-ADRDA), and how do these criteria relate to someone with a clinical diagnosis of Alzheimers?
Top of the list of outcomes in the methods section is 'dependency (institutionalisation)'. I agree this is an important outcome, and was therefore disappointed to find no further reference to this it in the results and discussion. Also, whether a person with Alzheimers can continue to live independently will depend to a considerable extent on the level of support provided by carers. It would be good to see a range of measures of dependency, including on carers, as outcomes. This issue is closely related to quality of life, both for the patient and the carer. For example, ability to shop and cook, clean, pay bills, maintain contact with friends and family, and to get out and about.

It is also hard to understand what many of the other listed outcomes mean for someone with Alzheimers. For example, what do 'global impression', 'functional performance', 'cognitive function (as measured by psychometric tests)' mean, and how do you plan to assess quality of life for both the person and their carer?
Much of the data in the review relates to scales with unpronounceable acronyms that I do not understand. What do these scales mean in terms of the important things in day to day life? What does worsening therefore mean in terms of loss of useful function?"

Reply

The main reviewer (J. Birks) replied:
We thank you for your comment on our review and are sorry that it did not answer many of the questions you have about treatment with donepezil.
The acronyms that you refer to (ICD-10, DSM and NINCDS-ADRDA) are those of diagnostic criteria. DSM refers to the 'Diagnostic and Statistical Manual of Mental Disorders'. NINCDS-ADRDA refers to the 'National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association'. ICD-10 refers to World Health Organisation classification of mental and behavioural disorders, the clinical description and diagnostic guidelines. References to these criteria are given in the review. The use of validated criteria such as these not only increases the accuracy of diagnosis but ensures standardisation between clinicians.
We agree that dependency is an important outcome and it was included in the protocol as an outcome of interest. Unfortunately none of the clinical trials of donepezil included in the review assessed this outcome and therefore there were no results on dependency.
The outcomes of the clinical trials are measured using validated cognitive tests and rating scales. Validation refers to the process of testing and subsequent publication of the results of the testing that a scale has to undergo before it is considered suitable to use in assessment. The publication will set out the exact method of applying and scoring the scale, together with the questionnaire if applicable. References to the scales that are used in the clinical trials included in the donepezil review are given, together with a short description of the scale within the methods section of the review. Some of these scales do attempt to measure the ability to carry out everyday activities.
In future we intend to bring together information on diagnostic criteria and rating scales on our website so that it is easily accessible.

Reply: Lelia Dudley to Jacqueline Birks

I do not think the response addresses my main questions, which were how do these criteria relate to someone with a clinical diagnosis of Alzheimers? And what do the outcomes reported mean to patients and their carers? Finally, within a systematic review, if dependency was identified as one of the main outcomes at the protocol stage, the lack of data makes it even more important that this lack is highlighted and taken account off in the discussion.

Reply: Jacqueline Birks to Lelia Dudley

The diagnostic criteria for the clinical diagnosis of Alzheimer's disease (NINCDS-ADRDA) require formal mental status testing, a medical history, physical neurological and psychiatric examination, laboratory tests and a scan. It would not be possible to include a lot of detail concerning the diagnostic criteria (DSM and NINCDS-ADRDA) in every review, but we are intending to put this information, together with detailed description of the commonly used rating scales and cognitive tests, on our website for those who are interested. This should also help readers assess the results from the clinical trials.
Dependency was not measured in any included trial, although some aspects of dependency are covered by rating scales that assess activities of daily living. It was listed under outcomes because we would have been interested in it if it were measured. If we had some measures of dependency and some data we would then be in a better position to discuss and comment on this outcome, but at the present time we have decided that we are not in a position to comment.

Contributors

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WHAT'S NEW

Last assessed as up-to-date: 20 May 2017.

Date	Event	Description
20 May 2017	New search has been performed	We carried out a top-up search on 20 May 2017. We have included 4 new studies, and the results and conclusions have changed
20 May 2017	New citation required and conclusions have changed	We carried out a top-up search for this review on 20 May 2017. We included new studies, results and conclusions have changed

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 3, 1998

Date	Event	Description
14 November 2016	New search has been performed	Updated search carried out.
9 February 2015	New search has been performed	Updated search carried out
7 June 2010	New search has been performed	Updated 2010 to include new search of 2009. Additional data were available in a new publication of Study 315 and Winblad 2005. 5 new studies were included
30 April 2009	Amended	An update search was performed for the review on 30 April 2009
4 November 2008	Amended	Converted to new review format.
19 May 2006	New search has been performed	May 2006: Two new trials have been included, both for severe dementia (MMSE <12)
13 September 2005	New citation required and conclusions have changed	Substantive amendment
26 November 2003	Feedback has been incorporated	Response to feedback added
25 August 2003	Feedback has been incorporated	feedback added

CONTRIBUTIONS OF AUTHORS

Hirukuni Beppu wrote the protocol, searched the Japanese literature, provided copies of the Japanese studies together with translations into English. Jacqueline Birks and David Melzer wrote the original review.

May 2003: Jacqueline Birks updated the review and analysed the data for the meta-analyses, and Richard Harvey replaced David Melzer as co-reviewer. He contributed to the background, the conclusions and discussion. Dymphna Hermans performed the update search.

October 2005: Jacqueline Birks updated the review and analysed the data for the meta-analyses. Richard Harvey contributed to the background, the conclusions and discussion. Dymphna Hermans performed the update search.

This review was peer reviewed in November 2005.

July 2010: Jacqueline Birks updated the review and analysed data for the meta-analyses. Anna Noel-Storr performed the update search.

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DECLARATIONS OF INTEREST

Jacqueline Birks: none known

Richard Harvey: none known

SOURCES OF SUPPORT

Internal sources

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JB receives salary support

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- University of Melbourne, Australia.
- Barwon Health, Australia.
- NIHR, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

When the protocol was written donepezil had received United States Food and Drug Administration (FDA) approval (1996) for mild and moderate dementia. Later studies were published that included participants with severe dementia and we included these studies in updated versions of the review. The FDA approved donepezil for people with severe dementia in 2006.

The methods for this current 2017 update of the review follow current Cochrane guidelines, which have changed substantially since the publication of the protocol and the first version of the review in 1998.

In the 2017 update of the review we reorganised the results to focus on the currently recommended dose. The main analysis was at 26 weeks and we prioritised seven outcomes for the meta-analyses.

We also expanded the 'Risk of bias' assessment of individual studies for this update, carrying out additional assessments on blinding, selective reporting and other biases.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy]; Cholinesterase Inhibitors [*therapeutic use]; Cognition Disorders [drug therapy]; Indans [*therapeutic use]; Nootropic Agents [*therapeutic use]; Piperidines [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans